VOL. 72 AUGUST, 1956 NO. 2

AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY

Editors

HOWARD C. TAYLOR, JR. WILLIAM J. DIECKMANN

OFFICIAL ORGAN

THE AMERICAN GYNECOLOGICAL SOCIETY
THE AMERICAN ASSOCIATION OF OBSTETRICIANS AND GYNECOLOGISTS
NEW YORK OBSTETRICAL SOCIETY; OBSTETRICAL SOCIETY OF PHILADELPHIA
BROOKLYN GYNECOLOGICAL SOCIETY; ST. LOUIS GYNECOLOGICAL SOCIETY
NEW ORLEANS GYNECOLOGICAL AND OBSTETRICAL SOCIETY
THE OBSTETRICAL AND GYNECOLOGICAL SOCIETY OF MARYLAND
CHICAGO GYNECOLOGICAL SOCIETY; CINCINNATI OBSTETRICAL AND GYNECOLOGICAL SOCIETY
CENTRAL ASSOCIATION OF OBSTETRICIANS AND GYNECOLOGISTS
AMERICAN BOARD OF OBSTETRICS AND GYNECOLOGY
WASHINGTON GYNECOLOGICAL SOCIETY
PITTSBURGH OBSTETRICAL AND GYNECOLOGICAL SOCIETY
OBSTETRICAL SOCIETY OF BOSTON
LOUISVILLE OBSTETRICAL AND GYNECOLOGICAL SOCIETY
SOUTH ATLANTIC ASSOCIATION OF OBSTETRICIANS AND GYNECOLOGISTS
SEATTLE GYNECOLOGICAL SOCIETY
SOCIETY OF OBSTETRICIANS AND GYNECOLOGISTS OF CANADA
ALABAMA ASSOCIATION OF OBSTETRICIANS AND GYNECOLOGISTS
AKRON OBSTETRICAL AND GYNECOLOGICAL SOCIETY
KANSAS CITY GYNECOLOGICAL SOCIETY
CENTRAL NEW YORK ASSOCIATION OF GYNECOLOGISTS AND OBSTETRICIANS
NEW JERSEY OBSTETRICAL AND GYNECOLOGICAL SOCIETY
IOWA OBSTETRIC AND GYNECOLOGIC SOCIETY
THE TEXAS ASSOCIATION OF OBSTETRICIANS AND GYNECOLOGISTS
OKLAHOMA CITY OBSTETRICAL AND GYNECOLOGICAL SOCIETY
MEMPHIS OBSTETRICAL AND GYNECOLOGICAL SOCIETY
UTAH OBSTETRICAL AND GYNECOLOGICAL SOCIETY
ROCHESTER OBSTETRICAL AND GYNECOLOGICAL SOCIETY
ARKANSAS OBSTETRICAL AND GYNECOLOGICAL SOCIETY

PUBLISHED BY THE C. V. MOSBY COMPANY, 3207 WASHINGTON BLVD., ST. LOUIS 3, U. S. A.

TABLE OF CONTENTS ON PAGE 6

Copyright © 1956 by The C. V. Mosby Company

JEANES HOSPITAL
Fox Chase
Philadelphia 11, Pa.

only pain is eliminated . . .

with HEAVY SOLUTION

Nupercaine®

When you provide saddle block anesthesia in obstetrical delivery, you assure "definite relief of pain . . . analgesia over the legs and thighs without causing paralysis of the muscles of the legs and thighs."[1]

Supplied: 1:400 Nupercaine hydrochloride in 5% dextrose, 2-ml. ampuls, each ml. containing 2.5 mg. Nupercaine and 50 mg. dextrose; cartons of 10.

1. Causey, P. S., Reed, W. A., and Ford, J. L.: Arizona Med. *8*:27 (Dec.) 1951.

CIBA SUMMIT, N. J.

2/2199M

Heavy Solution Nupercaine® hydrochloride (dibucaine hydrochloride with dextrose 5% CIBA).

Vol. 72, No. 2, August, 1956. American Journal of Obstetrics and Gynecology is published monthly by The C. V. Mosby Company, 3207 Washington Blvd., St. Louis 3, Mo. Subscription rates: United States and its Possessions $15.00, Students $7.50; Canada, Latin-America, and Spain $16.00, Students $8.50; Other Countries $17.50, Students $10.00. Single copies $2.50 postpaid. Entered as Second-Class Matter at Post Office at St. Louis, Mo., under Act of March 3, 1879. Printed in the U. S. A.

MEAD

Gravida II
Para I

...and on the go

Modern, active, on the go... and pregnant. That's why she needs a vitamin-mineral supplement generously formulated especially for the stress of pregnancy.

Natalins-PF and Natalins are designed for the busy, modern woman. Small in size, they're easy to take. Just 1 capsule t.i.d. provides more than ample nutritional support.

specify

Natalins-PF

Mead phosphorus-free prenatal vitamin-mineral capsules

Contain calcium... no phosphorus

or

Natalins®

Mead prenatal vitamin-mineral capsules

Contain both calcium and phosphorus

MEAD SYMBOL OF SERVICE IN MEDICINE

MEAD JOHNSON & COMPANY, EVANSVILLE 21, INDIANA, U.S.A.

only pain is eliminated . . .

with HEAVY SOLUTION

Nupercaine®

When you provide saddle block anesthesia in obstetrical delivery, you assure "definite relief of pain . . . analgesia over the legs and thighs without causing paralysis of the muscles of the legs and thighs."[1]

Supplied: 1:400 Nupercaine hydrochloride in 5% dextrose, 2-ml. ampuls, each ml. containing 2.5 mg. Nupercaine and 50 mg. dextrose; cartons of 10.

1. Causey, P. S., Reed, W. A., and Ford, J. L.: Arizona Med. *8*:27 (Dec.) 1951.

CIBA SUMMIT, N.J.

2/21908

Heavy Solution Nupercaine® hydrochloride (dibucaine hydrochloride with dextrose 5% CIBA).

Vol. 72, No. 2, August, 1956. American Journal of Obstetrics and Gynecology is published monthly by The C. V. Mosby Company, 3207 Washington Blvd., St. Louis 3, Mo. Subscription rates: United States and its Possessions $15.00, Students $7.50; Canada, Latin-America, and Spain $16.00, Students $8.50; Other Countries $17.50, Students $10.00. Single copies $2.50 postpaid. Entered as Second-Class Matter at Post Office at St. Louis, Mo., under Act of March 3, 1879. Printed in the U. S. A.

MEAD

Gravida II
Para I

...and on the go

Modern, active, on the go... and pregnant. That's why she needs a vitamin-mineral supplement generously formulated especially for the stress of pregnancy.

Natalins-PF and Natalins are designed for the busy, modern woman. Small in size, they're easy to take. Just 1 capsule t.i.d. provides more than ample nutritional support.

specify

Natalins-PF

Mead phosphorus-free prenatal vitamin-mineral capsules

Contain calcium... no phosphorus

or

Natalins®

Mead prenatal vitamin-mineral capsules

Contain both calcium and phosphorus

MEAD | SYMBOL OF SERVICE IN MEDICINE

MEAD JOHNSON & COMPANY, EVANSVILLE 21, INDIANA, U.S.A.

an important
first step
in the care
of the
infant's skin

DESITIN®
OINTMENT

No other product is more effective in healing the baby's skin and keeping it clear, smooth, supple, and free from

diaper rash • dermatitis • intertrigo
heat rash • chafing • irritation • excoriation

Soothing, protective, healing[1-5] Desitin Ointment — ***rich in cod liver oil*** — is the most widely used ethical specialty for the over-all care of the infant's skin.

Tubes of 1 oz., 2 oz., 4 oz., and 1 lb. jars.

May we send ***samples*** and literature?

DESITIN CHEMICAL COMPANY, Providence, R. I.

1. Grayzel, H. G., Heimer, C. B., and Grayzel, R. W.: New York St. J. Med. 53:2233, 1953. 2. Heimer, C. B., Grayzel, H. G., and Kramer, B.: Archives of Pediatrics 68:382, 1951. 3. Behrman, H. T., Combes, F. C., Bobroff, A., and Leviticus, R.: Ind. Med. & Surgery 18:512, 1949. 4. Sobel, A. E.: Scientific Exhibit, A.M.A. Meet. 1955. 5. Marks, M. M.: Missouri Med. 52:187, 1955.

new

A condensation of latest research findings on clinical aspects of Vitamin C

This just-completed, fact-packed, illustrated handbook summarizes ten years of research discoveries relating to vitamin C nutrition. More than 150 research reports are telescoped into 32 pages to make this an authoritative, succinct source for your reference library.

Up-to-date information is included on incidence of vitamin C deficiencies in various age groups . . . functions of vitamin C . . . Recommended Daily Allowances . . . nutritional values of fresh, canned, and frozen citrus . . . use of the "citrus snack" to step up vitamin C intake whenever indicated in therapeutic regimens.

Florida Citrus Commission, *Lakeland, Florida*

FLORIDA *Citrus*

ORANGES • GRAPEFRUIT • TANGERINES

For your free copy of
"Citrus Fruits in Health and Disease"

Florida Citrus Commission
Lakeland, Florida

Please send complimentary copy of new handbook "Citrus Fruits in Health and Disease".

name.....

street address.....

city.....*zone*.....*state*.....

Now you can add her stylish fancy to your prescription facts.

Soft plastic purse.
3 oz. tube of Lanteen jelly.
New Easy-clean jelly applicator.
Lanteen flat spring diaphragm of prescribed size.
Universal inserter.

The new Lanteen Exquiset reflects the best of milady's taste—it's both stylish and discreet. Your patient will appreciate your prescription for the Lanteen Exquiset. You will have prescribed an effective contraceptive technique, and also taken account of her feminine fancy. Another design by Lanteen for better patient-cooperation.

new! LANTEEN® *Exquiset*

Physician's prescription package.

*Lanteen jelly contains ricinoleic acid 0.50%, hexylresorcinol 0.10%, chlorothymol 0.0077%, sodium benzoate and glycerin in a tragacanth base. Lanteen jelly and flat-spring diaphragm sets are distributed by George A. Breon & Company, 1450 Broadway, New York 18, N. Y. (In Canada: E. & A. Martin Research Ltd., 20 Ripley Ave., Toronto, Canada.) Manufactured by Esta Medical Laboratories, Inc., Chicago 38, Ill. *Trademark of George A. Breon & Company.*

Latest clinical report on **Adrenosem®** *Salicylate*

(*brand of carbazochrome salicylate*)

The Use of the Systemic Hemostat Carbazochrome Salicylate

J. C. Bacala, M.D.

(*Abstracted from the Western Journal of Surgery, Obstetrics, and Gynecology, 64:88 (1956)*

The author emphasizes the need for dependable chemical control of bleeding and oozing, and reviews the methods that have been tried to attain hemostasis, including the use of vitamin K and bioflavonoids.

He gives the history of carbazochrome salicylate and describes the clinical work completed to demonstrate its effectiveness. It appears to be specific for conditions characterized by increased capillary permeability. It has no effect on large blood vessels; it does not alter blood components; it does not affect blood pressure or cardiac rate. It has neither vasoconstrictor or vasodilator action. The drug has no known contraindications.

He reviews 1051 cases from the files of St. Anthony Hospital, Louisville, Kentucky, of which 330 were treated with Adrenosem Salicylate. 317 were surgical cases and 13 obstetric-gynecological conditions. The treatment was given for symptomatic relief, and as a clinical recourse for patient safety.

In 1015 tonsillectomy patients the following results were noted: There was bleeding in 85 (19.8%) of 429 patients who received no medication. Patients who received a compound of oxalic and malonic acids numbered 115. Of these 16 (14%), developed bleeding. Of 248 patients receiving vitamin K preparations, 47 (19%) had postoperative hemorrhage. 233 patients received Adrenosem Salicylate. Of this group, only 16 (7%) had bleeding.

In other surgical conditions, Adrenosem was used successfully in gastrointestinal bleeding, cataract extraction, incisional seepage, and transurethral prostatectomy. It was also effective in 12 cases of epistaxis.

In the field of obstetrics and gynecology, Adrenosem controlled bleeding in menometrorrhagia, hymeneal laceration, cervical ooze, antepartum and postpartum bleeding, threatened abortion, and in two cases of surgery during pregnancy.

The author points out that in pregnancy, seepage bleeding occurs more because of capillary permeability, and in spite of increased coagulability. Here, Adrenosem becomes specific for strengthening capillary resistance.

Many of the observations in this study, however, involved bleeding incident to trauma of incision, retraction, dissection, tearing and stretching. In these conditions, he reasons that Adrenosem causes hemostasis by its effect on the capillary intercellular cement substance so that the cells draw closer together, and the ends of the capillaries constrict, causing a "self-clamping" mechanism.

The S. E. MASSENGILL company

Bristol, Tennessee New York Kansas City San Francisco

FILMS showing the uses of

Adrenosem®

Salicylate

(brand of carbazochrome salicylate)

in the control of bleeding

Films in color, demonstrating the uses of Adrenosem Salicylate* in surgery, are now available for showing to hospitals, medical societies and group meetings. Write to Film Division, S. E. Massengill Co., Bristol, Tennessee.

Send for comprehensive illustrated brochure describing the action and uses of this unique systemic hemostat.

INDICATED *preoperatively and postoperatively to control bleeding associated with:*

Tonsillectomy, adenoidectomy and nasopharynx surgery
Prostatic and bladder surgery
Dental surgery
Chest surgery and chronic pulmonary bleeding
Uterine bleeding and postpartum hemorrhage
Also: Idiopathic purpura, retinal hemorrhage, familial telangiectasis, epistaxis, hematuria

Supplied in ampuls, oral tablets and as a syrup.

The S. E. MASSENGILL company

BRISTOL, TENNESSEE • NEW YORK • KANSAS CITY • SAN FRANCISCO

**U. S. Pat. 2581850*

Mother and baby doing fine
after smoother labor and delivery
with THORAZINE*
as an adjuvant in obstetrics

Lessens anxiety, tension and fear; reduces the requirements for analgesics, sedatives and anesthetics; relieves suffering; minimizes the risk of over-sedated babies (barbiturates can often be eliminated); controls vomiting in all three stages of labor.

'Thorazine' is available in tablets, ampuls and syrup, as the hydrochloride; and in suppositories, as the base.

Smith, Kline & French Laboratories, Philadelphia

**T.M. Reg. U.S. Pat. Off. for chlorpromazine, S.K.F.*

CONTENTS FOR AUGUST, 1956

Original Communications

Catheterization Studies of Cardiac Hemodynamics in Normal Pregnant Women With Reference to Left Ventricular Work. David J. Rose, Mortimer E. Bader, Richard A. Bader, and Eugene Braunwald, New York, N. Y. ---- 233

Prophylactic Penicillin Administration in the Prevention of Perinatal Deaths. William C. Keettel, M.D., Iowa City, Iowa ---- 247

A Review of Vaginal Delivery Following Cesarean Section, From Private Practice. Paul E. Lawler, Sr., M.D., Matthew J. Bulfin, M.D., Frank C. Lawler, M.D., and Paul E. Lawler, Jr., M.D., Chicago, Ill. ---- 252

Dilatation of the Uterine Cervix of the Sow Following Treatment With Relaxin. M. X. Zarrow, Ph.D., G. M. Neher, Ph.D., D. Sikes, D.V.M., D. M. Brennan, M.S., and J. F. Bullard, D.V.M., Lafayette, Ind. ---- 260

Effects of Vitamin Deficiencies on Fertility, Course of Pregnancy, and Embryonic Development in Rats. Hilde Pfaltz, M.D., Basle, Switzerland, and Elmer L. Severinghaus, M.D., Nutley, N. J. ---- 265

Placenta Previa. Arthur M. Reich, M.D., New York, N. Y. ---- 277

Methyl Ergonovine (Methergine) in the Third Stage of Labor. Robert K. Ferguson, M.D., and Duncan E. Reid, M.D., Boston, Mass. ---- 290

A Study of Thirty-Eight Cases of Hydatidiform Mole at the Pennsylvania Hospital. Paul E. Stroup, M.D., Philadelphia, Pa. ---- 294

Therapeutic Abortion at the Chicago Lying-in Hospital. Myrna F. Loth, M.D., and H. Close Hesseltine, M.D., Chicago, Ill. ---- 304

Preterm Delivery of Erythroblastotic Infants. Tommy N. Evans, M.D., Ann Arbor, Mich. ---- 312

Repository Curare in Normal Obstetrics, a Controlled Study. Ellis N. Cohen, M.D., Hubert H. Theissen, M.D., and Joseph Marvin, M.D., St. Paul, Minn. ---- 323

Applications of the Reserve Midget Machine in Obstetrical Anesthesia. Vincent Tricomi, M.D., David P. Bauer, M.D., and Louis M. Hellman, M.D., Brooklyn, N. Y. ---- 326

Histogenesis of Degenerative Processes in the Normal Mature Placenta. Robert Burstein, M.D., Fred P. Handler, M.D., Samuel D. Soule, M.D., and Herman T. Blumenthal, M.D., St. Louis, Mo. ---- 332

Diagnosis and Obstetrical Treatment of Hydrocephalus. Matthew J. Bulfin, M.D., Frank C. Lawler, M.D., and Paul E. Lawler, Jr., M.D., Chicago, Ill ---- 343

A Critical Evaluation of Biological Pregnancy Tests. Rose L. Berman, B.A., New York, N. Y. ---- 349

The Incidence of Yeastlike Organisms in the Lower Genital Tract of Pregnant Filipino Women. Carlyn Halde, Ph.D., San Francisco, Calif., and Gloria T. Aragon, M.D., Manila, P. I. ---- 363

Management of Urinary-Vaginal Fistula in 253 Cases. Virgil S. Counseller, M.D., and Frank H. Haigler, Jr., M.D., Rochester, Minn. ---- 367

Experimental Evaluation of Three Types of End-to-End Ureteroureteral Anastomosis. N. S. R. Maluf, M.D., and Béla Halpert, M.D., Houston, Texas ---- 377

The Relationship of the Brenner Tumor to the Rete Ovarii, Grete Stohr, M.D., New York, N. Y. ---- 389

Glycogen in Invasive Squamous Carcinoma of the Uterine Cervix. Alvan G. Foraker, M.D., and Genevieve Marino, Jacksonville, Fla. ---- 400

Congenital Adrenal Hyperplasia (Pseudohermaphroditism) Before and After Cortisone Therapy. I. Adolescent Development and Menstruation. Elizabeth Knapp Smith, Ph.D., and Russell R. de Alvarez, M.D., Seattle, Wash. ---- 404

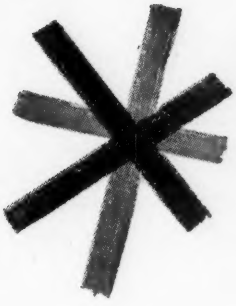
The Treatment of Premenstrual Tension With a Combination of an Antihistaminic and a Theophylline Derivative. Thomas H. McGavack, M.D., Herbert J. Spoor, M.D., Martin L. Stone, M.D., and Sidney Pearson, Ph.D., New York, N. Y. ---- 416

Department of Case Reports, New Instruments, Etc.

Bilateral Ligation of the Common Iliac Vein at the Time of Cesarean Section. Robert W. Kistner, M.D., and Christopher J. Duncan, M.D., Brookline, Mass. -- 423

Massive Thrombophlebitis of the Ovarian Vein. O. G. Austin, Medina, Ohio ---- 428

(Continued on page 8)



EASIER CONTROL OF SUMMER-TIME ALLERGIES

For the quick relief which ACTH gives in summer-time allergies, with minimal inconvenience to your patient, use Cortrophin-Zinc. Its prolonged action permits maximal response in rose fever, poison ivy, poison oak, sumac, asthma, and other allergic manifestations, with fewer injections. Each injection lasts at least 24 hours in the most acute cases to 48 and even 72 hours in milder cases. And Cortrophin-Zinc is easy to use, being an aqueous suspension which requires no preheating and flows easily through a 26-gauge needle.

CORTROPHIN*-ZINC†

HAY FEVER
POISON IVY
POISON OAK OR SUMAC
SEASONAL ASTHMA
ROSE FEVER

Supplied in 5-cc vials, each cc containing 40 U.S.P. units of corticotropin adsorbed on zinc hydroxide (2.0 mg zinc/cc)

**T.M.—Cortrophin*

†*Patent Pending. Available in other countries as Cortrophine-Z.*

†*Organon brand of Corticotropin-Zinc Hydroxide*

an Organon *development*

ORGANON INC. • ORANGE, N. J.

CONTENTS (*Continued from page 6*)

A Case of Interstitial Tubal Pregnancy With Rupture into the Bowel. Augusta Webster, M.D., and Charlotte Herman Kerr, M.D., Chicago, Ill. ---------- 430

Ectopic Pregnancy Followed by Two Recurrences. Henry B. Turner, M.D., and T. Murray Ferguson, M.D., Memphis, Tenn. ---------- 433

Deaths of Two Consecutive Infants Born of a Myasthenic Mother. Alex J. Arieff, M.D., and W. R. Roach, M.D., Chicago, Ill. ---------- 435

Tuberculous Meningitis and Pregnancy. H. G. K. Faaland, Commander (MC) USN 437

Renal-Cell Carcinoma Complicated by Pregnancy. Harry K. Waddington, M.D., Chicago, Ill. ---------- 441

A Case of Hypofibrinogenemia Following Vaginal Surgery. William J. Sweeney, M.D., New York, N. Y. ---------- 446

Adenocarcinoma of the Appendix With Krukenberg Tumor of the Ovaries. Richard M. Nunnally, M.D., and P. O'B. Montgomery, M.D., Dallas, Texas ---------- 449

An Instrument to Aid in Vaginal Plastic Surgery. John C. Bodle, M.D., Salt Lake City, Utah ---------- 453

Myoma of the Vagina. David M. Farell, M.D., and Jerome Abrams, M.D., Philadelphia, Pa. ---------- 455

Department of Reviews and Abstracts

Selected Abstracts ---------- 457

Correspondence

Correspondence ---------- 465

(See page 40 for Editorial and Business Communications)

American Journal of Obstetrics and Gynecology

Editors: HOWARD C. TAYLOR, JR., and WILLIAM J. DIECKMANN

ADVISORY COMMITTEE ON POLICY 1956

Willard M. Allen
John I. Brewer
Francis Bayard Carter
Conrad G. Collins
Nicholson J. Eastman
Frank R. Lock
Newell W. Philpott
John Rock
Donald G. Tollefson

ADVISORY EDITORIAL COMMITTEE 1956

Albert H. Aldridge
Edward Allen
Allan C. Barnes
Leroy A. Calkins
Russell R. de Alvarez
R. Gordon Douglas
George H. Gardner
Louis M. Hellman
Carl P. Huber
Frank R. Lock
Curtis J. Lund
Andrew A. Marchetti
Harvey B. Matthews
John L. McKelvey
Charles E. McLennan
Joe Vincent Meigs
William F. Mengert
Norman F. Miller
Thaddeus L. Montgomery
Daniel G. Morton
Emil Novak
Ernest W. Page
Franklin L. Payne
Lawrence M. Randall
Duncan E. Reid
Ralph A. Reis
Herbert E. Schmitz
George V. Smith
Wm. E. Studdiford
E. Stewart Taylor
Richard W. Te Linde
Herbert F. Traut

for the modern woman...a modern prenatal supplement

Today's pregnant woman is more fortunate than her sister of yesteryear . . . she looks better, feels better and enjoys greater freedom during her pregnancy. She is free, too, from such traditional prenatal distress as leg cramps, irritability and mild edema when a *modern* prenatal supplement is prescribed.

Usable calcium—Recent evidence points to a new rationale of prenatal nutrition. ". . . it is apparent that dicalcium phosphate, so widely used as a dietary supplement in pregnancy, is undesirable."* Calcisalin, for routine prenatal supplementation, provides calcium in the *usable* form of the lactate salt, rather than phosphate.

The complete prenatal supplement – Calcisalin also provides reactive aluminum hydroxide gel (to absorb excess dietary phosphorus) and the minimum daily vitamin and iron allowances for pregnancy as recommended by the National Research Council.

Thus the risk of inadvertently raising the phosphorus level to the point where it interferes with calcium absorption is avoided with Calcisalin.

Dosage: Two tablets three times daily after meals. *Available:* Bottles of 100 tablets and 8-oz. reusable nursing bottles containing 300 tablets.

*Page, E. W., and Page, E. P.: Obstet. & Gynec. *1*:94 (Jan.) 1953.

Calcisalin®

WARNER-CHILCOTT

A New Narcotic Antagonist with Unique and Important Advantages

LORFAN 'Roche'

In proper dosage, prevents or reverses narcotic-induced respiratory depression *without* inhibiting pain relief

Non-narcotic

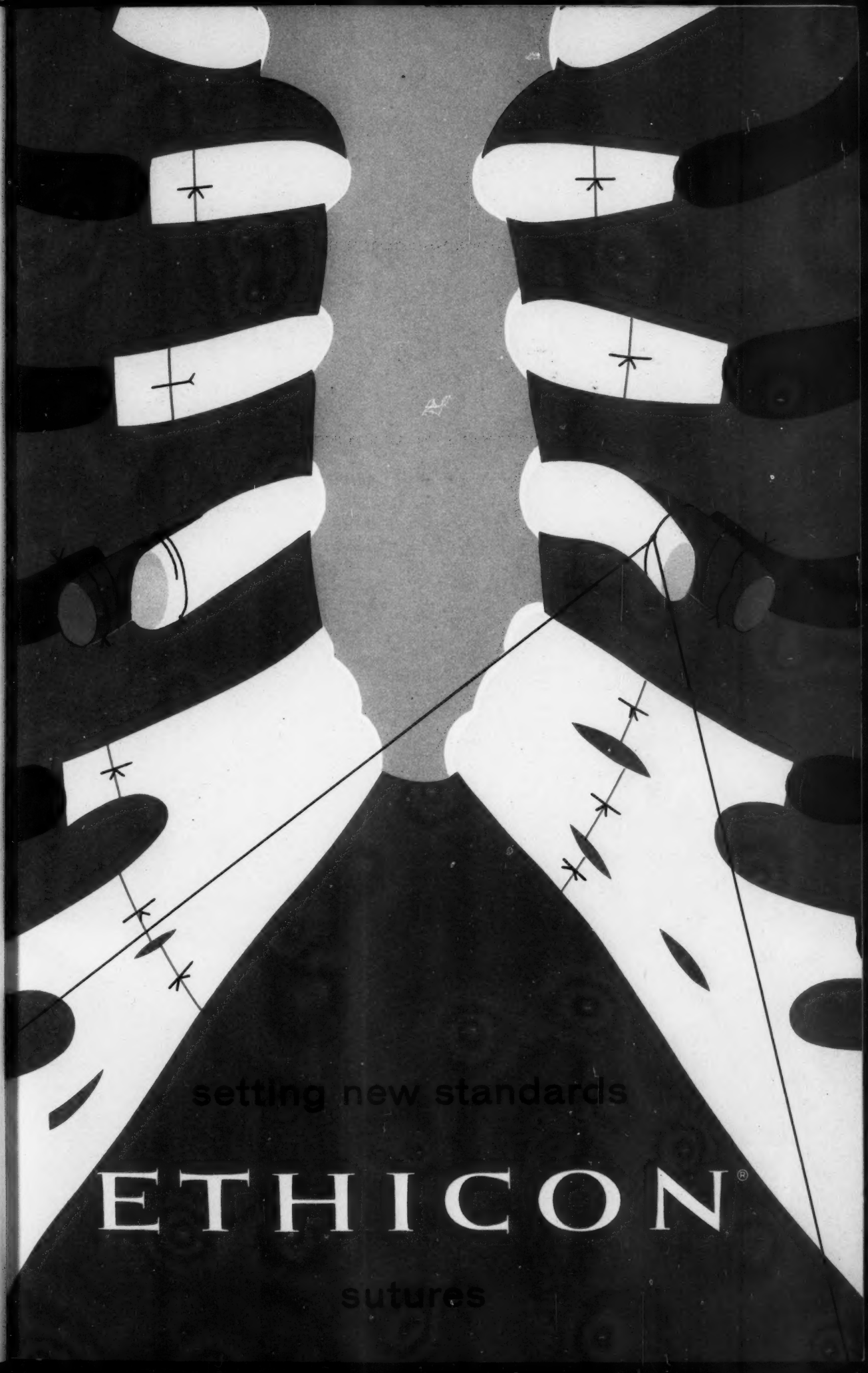
Acts for 2 to 5 hours

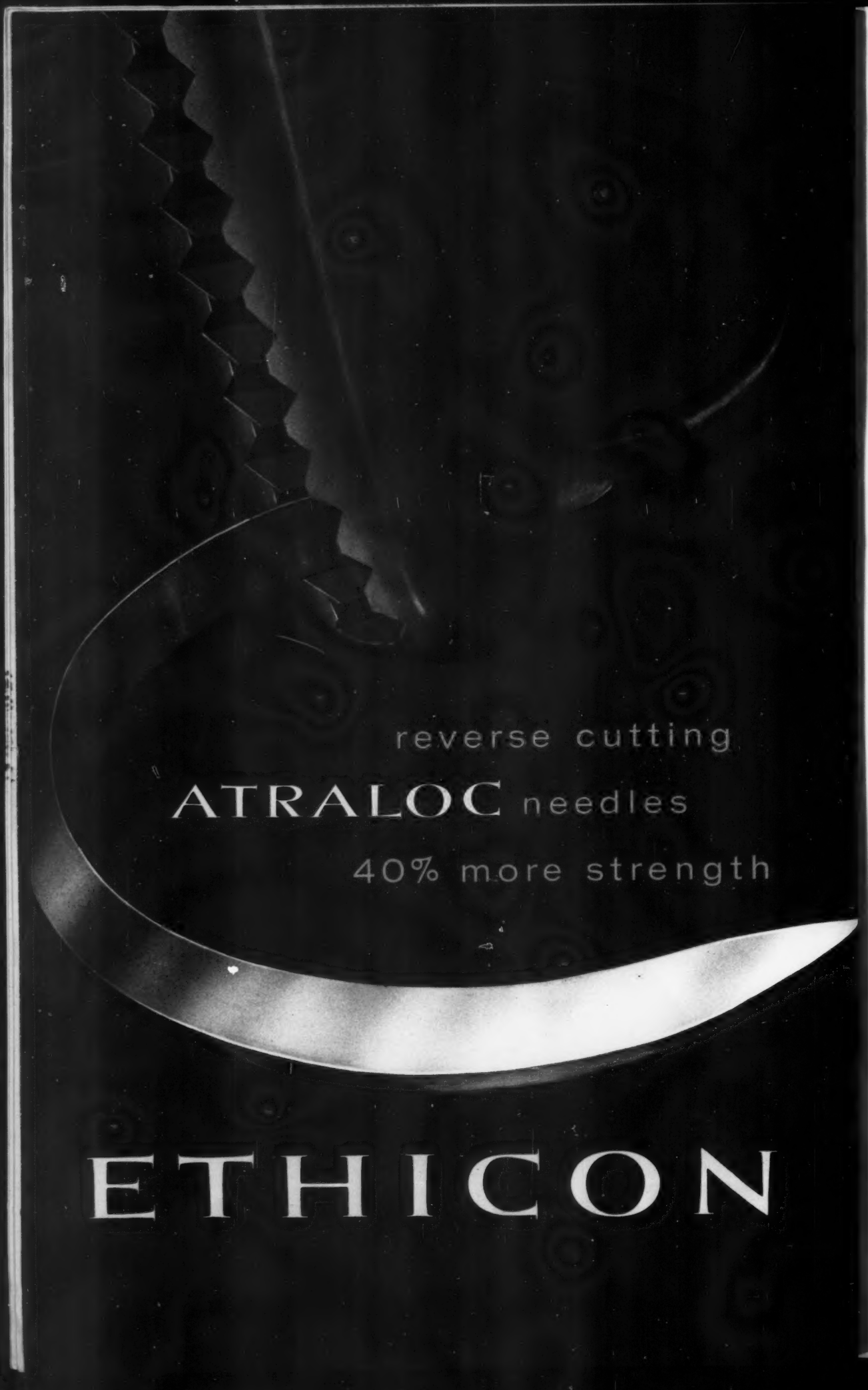
One mg is equivalent to at least 5 mg nalorphine

Lorfan will counteract the depressant effects of synthetic narcotics such as Levo-Dromoran,® Nisentil,® meperidine, methadone, as well as the natural opiates – morphine, dihydromorphinone, Pantopon®.
May be used in combination with narcotics for preoperative preparation, postoperative pain, supplementation of nitrous oxide-oxygen anesthesia, obstetrics.

Lorfan™ Tartrate – brand of levallorphan tartrate

Original Research in
Medicine and Chemistry


setting new standards
ETHICON®
sutures


reverse cutting
ATRALOC needles
40% more strength
ETHICON

90-95% effective,[1-2] "no side effects were observed"[2] one tablet at bedtime

1. Groskloss, H. H. et al: Bonadoxin®: a unique control for nausea and vomiting of pregnancy. Clin. Med. 2:885 (Sept.) 1955. 2. Tartikoff, G.: The antiemetic function of Bonadoxin in the nausea and vomiting of pregnancy. Clin. Med. 3:223 (Mar.) 1956.

ROERIG Rx

Chicago 11, Ill.

LOCAL ESTROGEN APPLICATION GREATLY SIMPLIFIES TREATMENT OF SENILE VAGINITIS

THIS method provides an "almost immediate healing and soothing effect" Doyle reports,[1] and "is a valuable therapeutic constituent in the management of vaginitis and vaginal infections, regardless of etiology."[2] This worker employed "Premarin" Vaginal Cream applied locally and found it "superior" to the use of suppositories. There were none of the "side-effects frequently noted with synthetic products . . ."[1]

Favors Rapid Healing in Vaginal Surgery

In plastic vaginal surgery in the postmenopausal patient, local estrogen application prior to and after intervention will restore the atrophic and friable mucosa to a more youthful state by promoting proliferation and vascularity of the epithelium. This will facilitate the surgical procedure as well as favor more rapid healing.[2,3]

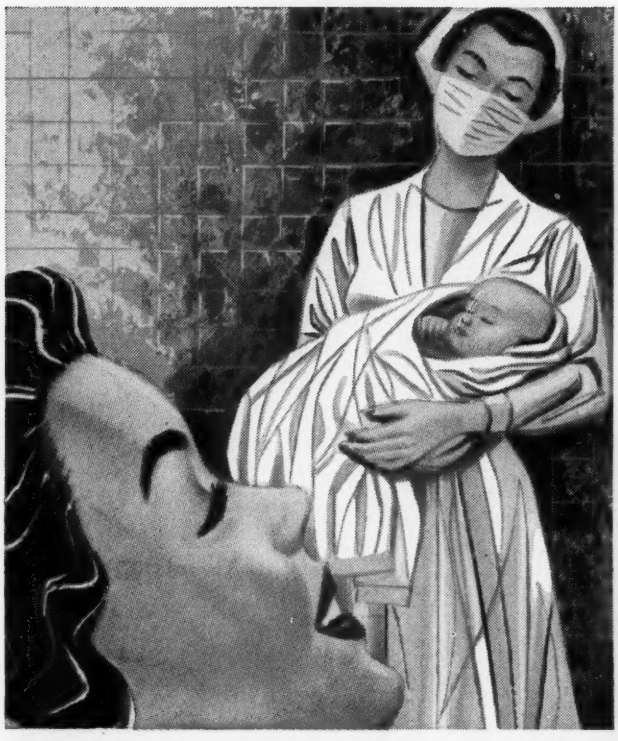
"PREMARIN" VAGINAL CREAM in a nonliquefying base, is standardized in terms of the weight of active, water-soluble estrogen content expressed as sodium estrone sulfate (0.625 mg. per gram). Presented in a combination package No. 874 — 1½ oz. tube with specially designed calibrated applicator; also refill available. Complete information may be obtained by writing to Ayerst Laboratories, 22 East 40th Street, New York 16, N. Y.

1. Doyle, J. C.: California Med. *71*:15 (July) 1949. • 2. Doyle, J. C.: Urol. & Cutan. Rev. *55*:618 (Oct.) 1951. • 3. Hamblen, E. C., in Stieglitz, E. J.: Geriatric Medicine, ed. 2, Philadelphia, W. B. Saunders Company, 1949, p. 657.

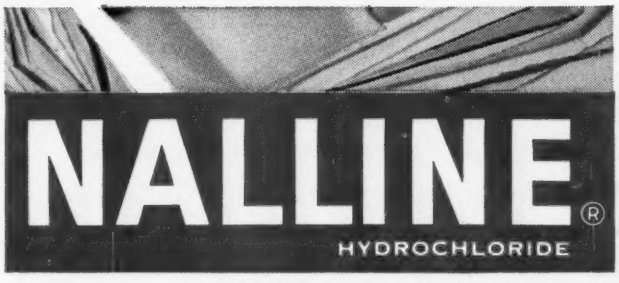
"Premarin" Vaginal Cream

Ayerst Laboratories • New York, N. Y. • Montreal, Canada

5650



Routine prophylaxis against over-narcosis



(NALORPHINE HYDROCHLORIDE U.S.P., MERCK)

When narcotics are a standard part of the obstetrical preparation, prophylactic use of NALLINE offers many benefits. Injected five to fifteen minutes before delivery, NALLINE reduces significantly the need for resuscitation and time required for the newborn infant to gasp and cry. In the mother, NALLINE combats narcotic-induced respiratory and circulatory depression and facilitates induction of inhalation anesthesia. NALLINE antagonizes morphine, heroin, methadone, Dromoran®, Levo-Dromoran®, Nisentil®, Dilaudid®, Pantopon®, and Demerol®.

Supplied: In 1-cc. and 2-cc. ampuls (5 mg./cc.). Also, in 1-cc. ampuls (0.2 mg./cc.) for neonatal use. NALLINE comes within the scope of the Federal Narcotic Law.

MSD

MERCK SHARP & DOHME

DIVISION OF MERCK & CO., INC., PHILADELPHIA 1, PA.

"Doctor, I feel like screaming or crying all day long . . ."

Many physicians have found that 'Thora-Dex' is of particular value in the treatment of mental and emotional disorders which, while severe, are not such that the patient needs to be hospitalized.

Typically, the patient treated with 'Thora-Dex' will be calm yet alert, relaxed yet energetic—better able to perform her daily duties, to face her responsibilities, and to continue normal social activities.

THORA-DEX*

a balanced combination of Thorazine† and Dexedrine‡

'Thora-Dex' Tablets are available in two strengths:

SKF 1 — 10 mg. of 'Thorazine' plus 2 mg. of 'Dexedrine'

SKF 2 — 25 mg. of 'Thorazine' plus 5 mg. of 'Dexedrine'

'Thora-Dex' should be administered discriminately and, before prescribing, the physician should be fully conversant with the available literature.

Smith, Kline & French Laboratories, Philadelphia

*Trademark †T.M. Reg. U.S. Pat. Off. for chlorpromazine, S.K.F.
‡T.M. Reg. U.S. Pat. Off. for dextro-amphetamine sulfate, S.K.F.

In deference to her daintiness . . .

- Massengill Powder is buffered to *maintain** an acid condition in the vaginal mucosa.
- Massengill Powder has a low surface tension which enables it to penetrate into and cleanse the folds of the vaginal mucosa.
- Massengill Powder has a "clean" antiseptic fragrance. It enjoys unusual patient acceptance.
- Massengill Powder solutions are easy to prepare. They are nonstaining, mildly astringent.

massengill powder®

when recommending a vaginal douche

indications:

Massengill Powder solutions are a valuable adjunct in the management of monilia, trichomonas, staphylococcus, and streptococcus infections of the vaginal tract. Routine douching with Massengill Powder solutions minimizes subjective discomfort and maintains a state of cleanliness and normal acidity without interfering with specific treatment.

*In a recent clinical report, ambulatory patients—with an alkaline vaginal mucosa resulting from pathogens—maintained an acid vaginal mucosa of pH 3.5 for 4 to 6 hours after douching with Massengill Powder; recumbent patients maintained a satisfactory acid condition up to 24 hours.

Generous samples on request.

The S. E. MASSENGILL Company

Bristol, Tennessee *New York* *Kansas City* *San Francisco*

* T-C JAWS

another development by SKLAR

* *Sklar Needle Holders incorporate Tungsten Carbide (T-C) as an integral part of the jaws. This revolutionary development eliminates the many disadvantages of welded inserts.*

NEEDLE HOLDERS WITH TC-JAWS
(Pat. Appl'd. for)
Crile
Baumgartner
New Orleans
Mayo 6"—7"—8"
Masson
Sarot
Collier
Heaney

Stainless Steel

T-C Jaws Assure....

POSITIVE GRIP . . . The extremely hard surface and extra fine serrations prevent rotation of suture needles without indenting the surface.

DEPENDABILITY . . . No inserts to loosen or fall out . . . original temper and strength of jaws is preserved.

To distinguish T-C Needle Holders from the standard instruments, the handles are copper plated for ready identification.

These superior and dependable instruments are priced slightly higher than our standard pattern Needle Holders.

Available through accredited surgical supply distributors

Sklar LONG ISLAND CITY, NEW YORK

in 1 tablet

bacterial + symptomatic

control

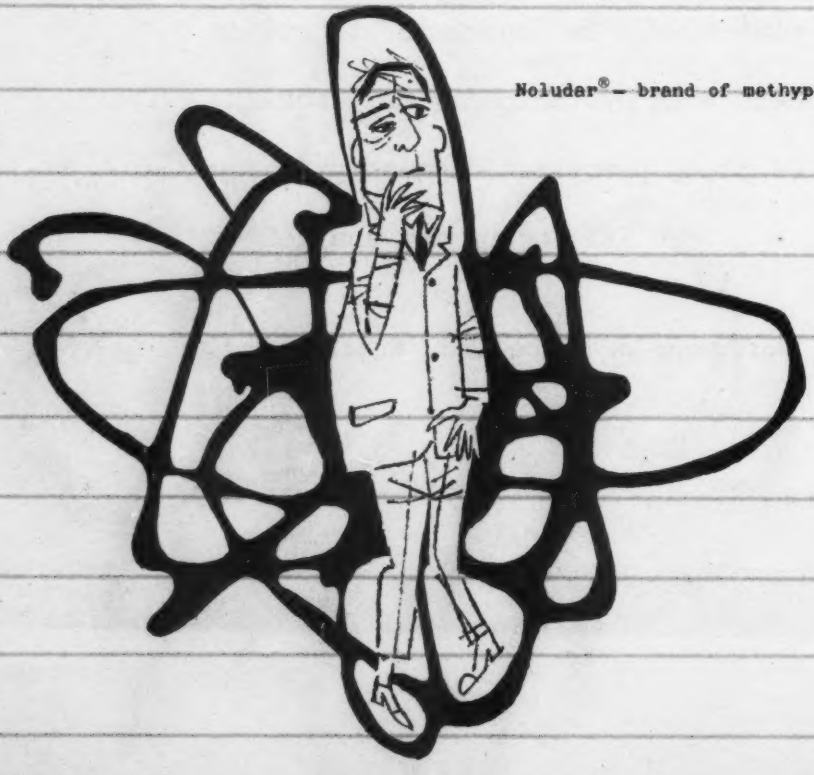
of Urinary Infections

Azo Gantrisin contains, in each tablet, 0.5 Gm Gantrisin® to attack pathogens both systemically and locally, plus 50 mg phenylazo-diamino-pyridine HCl for prompt analgesia.

Hoffmann-La Roche Inc, Nutley, N.J.

For patients wound up in a tangle of nerves—

Noludar 'Roche' provides relaxation. Not a barbiturate, not habit forming, 50 mg t.i.d. brings daytime sedation without undue drowsiness, while 200 mg h.s. usually induces a restful night's sleep with a clear-headed awakening. Noludar tablets, 50 and 200 mg; elixir, 50 mg per teaspoonful. Hoffmann-La Roche Inc, Nutley, N.J.



Noludar®— brand of methyprylon

The Advantages of Rauwiloid-Based Combination Therapy

In Difficult-to-Manage HYPERTENSION

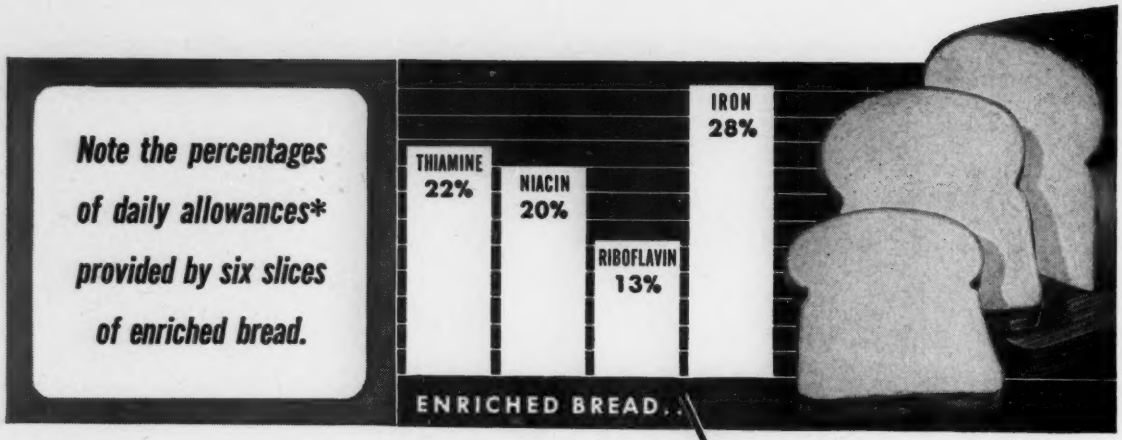
Rauwiloid® + Veriloid®

For moderate to severe hypertension. The combination permits long-term therapy with lower doses of Veriloid, greatly lessened side effects, and dependably stable response. Each tablet contains 1 mg. Rauwiloid (alseroxylon) and 3 mg. Veriloid (alkavervir). Initial dose, 1 tablet t.i.d., p.c.

Rauwiloid® + Hexamethonium

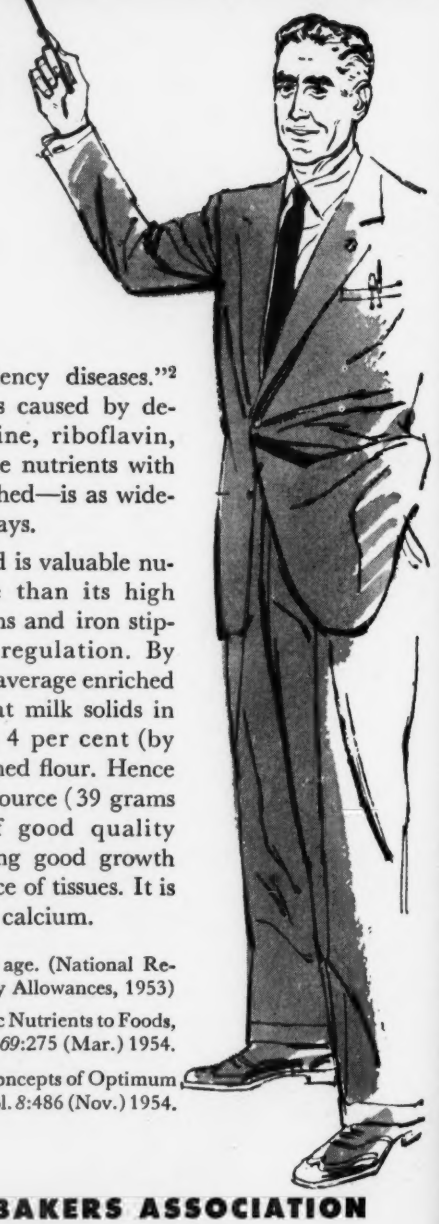
For severe, otherwise intractable hypertension, this single-tablet combination provides smoother, less erratic response to oral hexamethonium, thereby stabilizing reduced tension. Permits up to 50% less hexamethonium to exert full effect. Each tablet contains 1 mg. Rauwiloid and 250 mg. hexamethonium chloride dihydrate. Initial dose ½ tablet q.i.d.

Riker LOS ANGELES



enriched bread

endorsed again by authorities on public health



ENRICHED BREAD, marketed since 1941, recently has been endorsed again by the Food and Nutrition Board of the National Research Council and by the Council on Foods and Nutrition of the American Medical Association.[1] This reaffirmation of endorsement in former years (1939, 1941, 1946) is based on "good evidence" that enriched bread has been "beneficial to the public," has "encouraged sound nutritional practices," and has contributed notably to "correcting deficiencies in the diets of the general population."

Nationally marketed enriched bread merits a large share of the credit for "the great gain in public health" in recent years, attributed to modern food commodities possessing high nutrient content. "Within the past two decades, for the first time in our history we have reached a national pattern of food practices that permits almost a complete escape from the classical forms of nutritional deficiency diseases."[2] None of the diseases caused by deficiencies of thiamine, riboflavin, niacin, and iron—the nutrients with which bread is enriched—is as widespread as in former days.

But enriched bread is valuable nutritionally for more than its high amounts of B vitamins and iron stipulated by official regulation. By commercial practice, average enriched bread contains nonfat milk solids in amounts averaging 4 per cent (by weight) of its contained flour. Hence it also represents a source (39 grams per pound loaf) of good quality protein for supporting good growth as well as maintenance of tissues. It is also a good source of calcium.

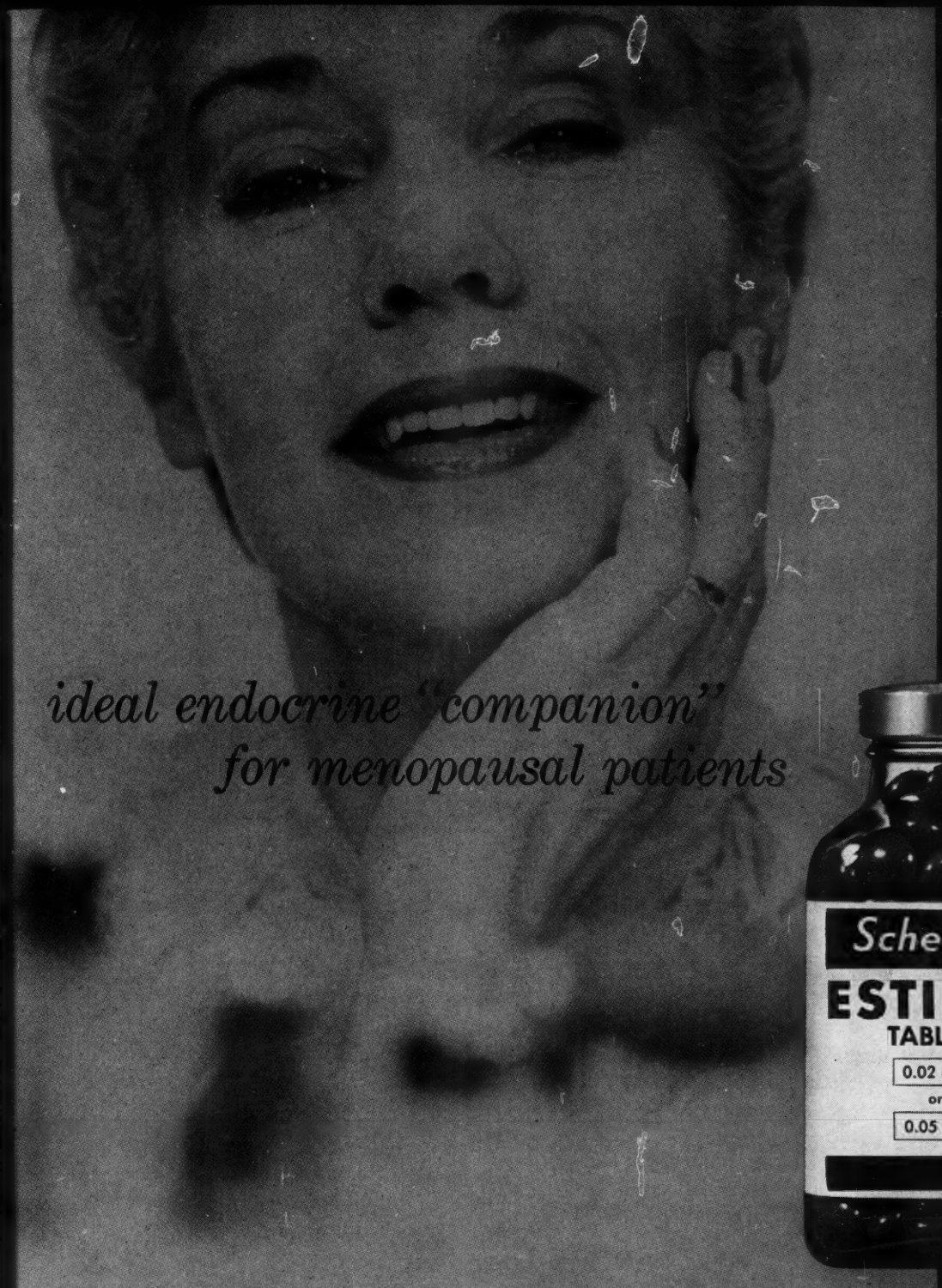
*For man 45 years of age. (National Research Council Dietary Allowances, 1953)

1. The Addition of Specific Nutrients to Foods, Public Health Reports *69*:275 (Mar.) 1954.

2. King, C. G.: Newer Concepts of Optimum Nutrition, Food Technol. *8*:486 (Nov.) 1954.

The nutritional statements made in this advertisement have been reviewed and found consistent with current medical opinion by the Council on Foods and Nutrition of the American Medical Association.

AMERICAN BAKERS ASSOCIATION
20 NORTH WACKER DRIVE, CHICAGO 6, ILL.



ideal endocrine "companion"
for menopausal patients

comforts—Controls major symptoms within 6 to 10 days, hot flushes in as few as 3 days.

cheers—Confers a welcome feeling of physical vitality and mental well-being.

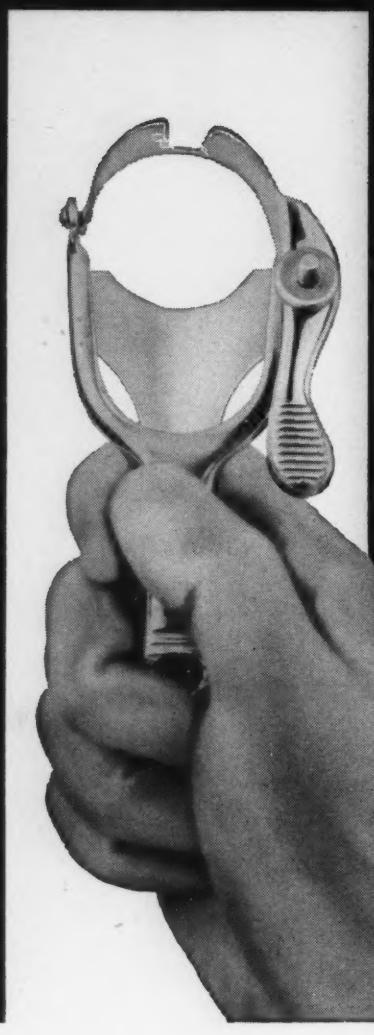
compatible—Much less prone to cause the side effects so often experienced with stilbene derivatives.

thrifty—Does "a better job at far less cost" and is "much better to use than any of the so-called naturally conjugated estrogens."*

*Clinton, M., Round Table Discussion: New York J. Med. *54*:481, 1954.
ESTINYL,® brand of Ethinyl Estradiol U.S.P.

EE-J-61 356

AN ADVANCE



in the treatment of vaginitis

new . . . simple . . . effective . . . topical therapy

Clinical evidence shows Sterisil Vaginal Gel to be highly effective not only against Trichomonas and Monilia, but against the newly discovered pathogen *Hemophilus vaginalis* (now believed to be the etiologic organism most frequently responsible for so-called "nonspecific" vaginitis and leukorrhea).*

High tissue affinity of Sterisil assures prolonged antiseptic action; vaginal secretions are less likely to remove Sterisil from the site of application. Sterisil is also more convenient for the patient. Fewer applications are required for successful treatment.

Acceptable to patients, Sterisil Vaginal Gel is easily applied, won't leak or stain, requires no pad. Signs of local or systemic toxicity or sensitization have not been reported.

Dosage: One application every other night until a total of 6 has been reached. This treatment may be repeated if necessary.

Supplied in 1½ oz. tube with 6 disposable applicators. Instructions for use are included with each package.

*Gardner, H. L., and Dukes, C. D.: Am. J. Obst. & Gynec. *69*:962 (May) 1955.

STERISIL® VAGINAL GEL

Brand of hexetidine

WARNER-CHILCOTT

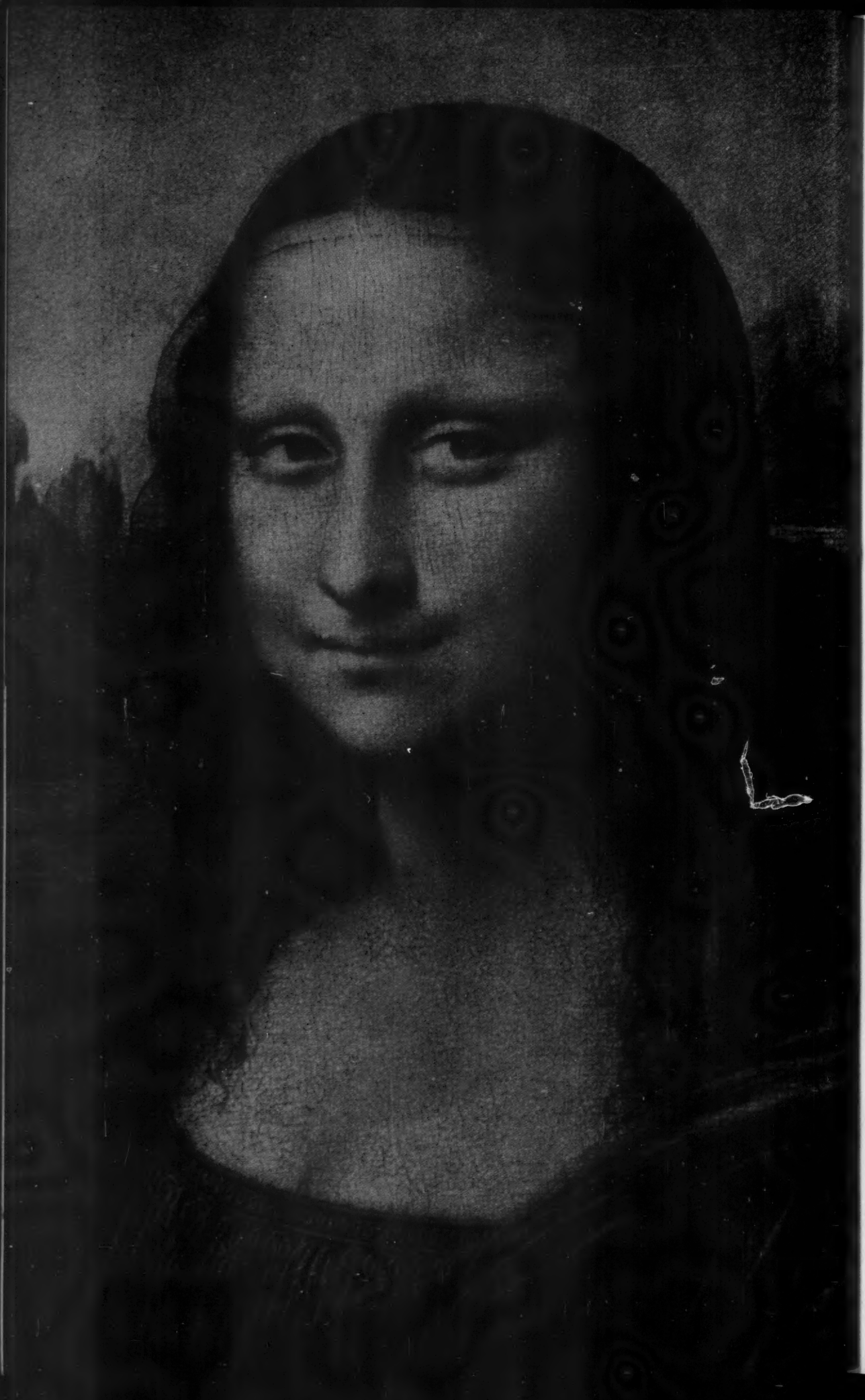
more hemoglobin in less time

Rarical® TABLETS

a unique <u>new</u> compound, ferrous calcium citrate, with tricalcium citrate

- iron and calcium in one molecule
- iron your patients can tolerate
- no leg cramps with this iron-calcium

Ortho



A SMILE AGAIN IN JUST 12 DAYS WITH TIME-SAVING

Trīva

the MODERN treatment for all 3 types of vaginitis

TRIVA effectively annihilates vaginal microorganisms, restores mucosal integrity and accelerates healing for rapid recovery. Non-irritant, non-toxic, non-staining, TRIVA is a safe, vaginal douche... even during pregnancy. Effective in any pH medium. Most cases of trichomonal, monilial and non-specific vaginitis become asymptomatic and organism free in 6 to 12 days. Simple to prescribe! Just write: "TRIVA (Boyle) sig; douche b.i.d. for 12 days." For complete data see Physicians' Desk Reference, 1956, page 427.

AVAILABLE AT ALL PHARMACIES, in convenient packages of 24 individual 3 Gm. packets, each containing 35% Alkyl Aryl sulfonate, (surface-active, germicidal and detergent), 0.33% Disodium ethylene bis-iminodiacetate (chelating agent), 53% Sodium sulfate, 2% Oxyquinoline sulfate (bactericide, protozoacide) and 9.67% dispersant.

Full treatment package and literature on request.

BOYLE

BOYLE & COMPANY *Bell Gardens, California*

+

B_6

Striking relief from nausea of pregnancy

'MAREDOX'

brand Cyclizine Hydrochloride and
Pyridoxine Hydrochloride

Just one tablet a day, on rising or at night, restores the nausea-free status to most pregnant women.

Each tablet of 'Maredox' contains:
'Marezine'® brand
Cyclizine Hydrochloride . . . . . 50 mg.
Pyridoxine Hydrochloride . . . . . 50 mg.

BURROUGHS WELLCOME & CO. (U. S. A.) INC., Tuckahoe, New York

NEW

HOW TO COMFORT THE OB PATIENT AND SAVE NURSING TIME

In the past two years, hundreds of hospitals have adopted Americaine Aerosol as the routine spray-on relief for painful post-episiotomies, tender hemorrhoids, and fissured nipples.

Americaine Aerosol is the first aerosol preparation to be provided for this use. It offers the same potent topical agent as Americaine Ointment (20% dissolved benzocaine), and it is quick, easy to apply, and sanitary.

HOW TO GET BEST RESULTS AND ECONOMY IN APPLICATION

Americaine Aerosol is so easy to use, it can be applied by the nurse or by the patient, herself: Hold dispenser 8″ to 12″ from area and press button to release spray. Spray sufficient to give good coverage without waste. Do not apply pad or other dressing for about 5 to 10 minutes after application, as this may soak up some of the medication and reduce effect. Do not hold dispenser upside down.

AMERICAINE AEROSOL FEATURES THAT MERIT YOUR ATTENTION

1. Americaine provides relief in 2-3 minutes. Relief usually lasts 4-6 hours.
2. Americaine Aerosol should not be confused with any other aerosols or topical analgesics containing a much lower percentage of active drug. Only Americaine contains 20% dissolved benzocaine for faster, more prolonged relief.
3. Americaine is a simple, uncomplicated formula. This minimizes possibility of sensitivity. Not a single case of sensitivity was reported in 1866 published clinical cases. (Reprints on request.)

THERE IS A FREE AMERICAINE AEROSOL FOR YOU
Please enclose prescription blank when requesting

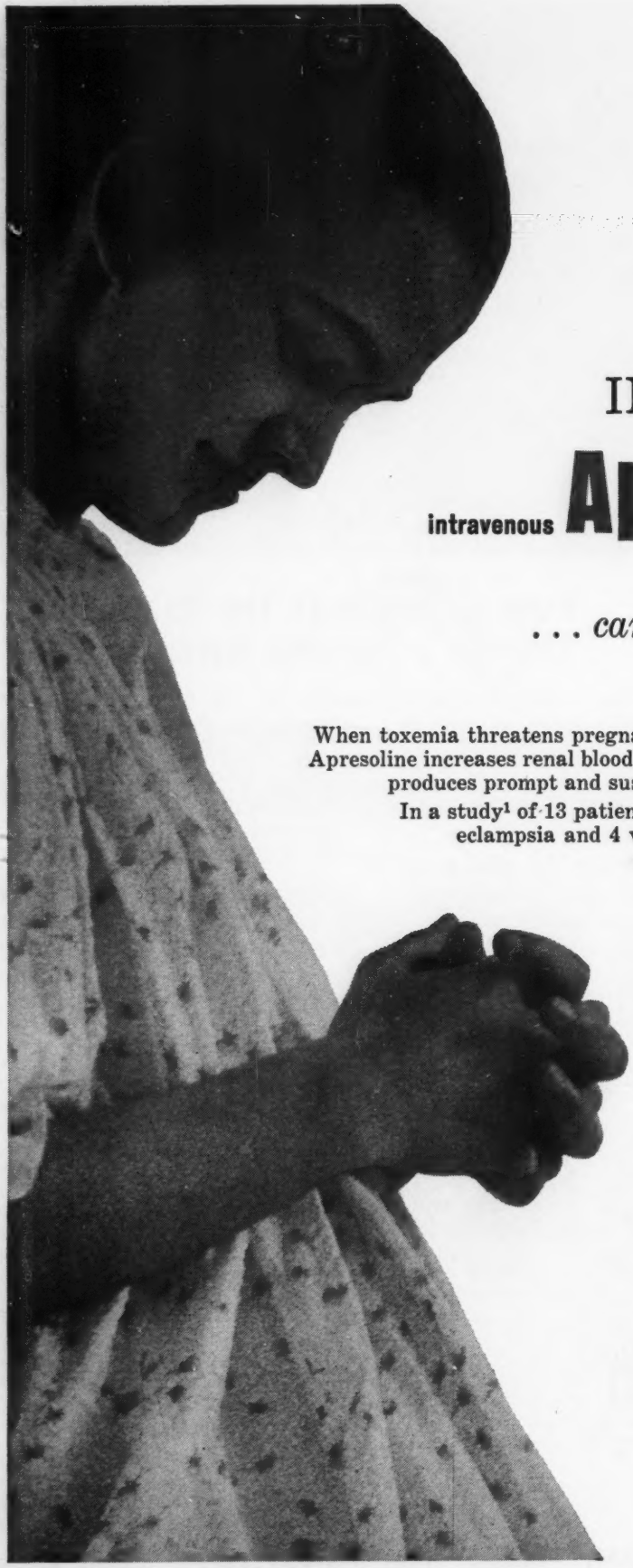
SMALL SIZE !

New 3 oz. dispenser is easy for patient to use.

Americaine
AEROSOL

NOW, THREE SIZES: 11 oz. size for professional use and floor stock. 5.5 oz. and 3 oz. sizes for your prescriptions.

ARNAR-STONE LABORATORIES, INC., Mount Prospect, Illinois



to avert the perils of

TOXEMIA IN PREGNANCY

intravenous **Apresoline®**

hydrochloride

(hydralazine hydrochloride CIBA)

. . . can dramatically reduce high blood pressure

When toxemia threatens pregnancy, Apresoline can be life-saving. Apresoline increases renal blood flow, decreases vascular resistance, produces prompt and sustained reduction of blood pressure.

In a study[1] of 13 patients with severe preeclampsia, 1 with eclampsia and 4 with preeclampsia superimposed on essential hypertension, intravenous Apresoline effectively reduced pressure. Kistner administered 40 mg. initially and, depending on response, additional doses of 20 to 40 mg. Average maximum decrease during treatment was 57 mm. Hg systolic, 48 mm. Hg diastolic. Intravenous Apresoline held diastolic pressure under 100 for 4½ hours in one toxemic patient and both systolic and diastolic pressures remained below control levels for more than 6 hours.

1. Kistner, R. W.: J. Obst. & Gynaec. Brit. Emp. *61*:463 (Aug.) 1954.

SUPPLIED: *Ampuls*, 1 ml., 20 mg. per ml. *Tablets*, 10 mg. (yellow, double-scored), 25 mg. (blue, coated), 50 mg. (pink, coated); bottles of 100, 500 and 1000. *Tablets*, 100 mg. (orange, coated); bottles of 100 and 1000.

CIBA

SUMMIT, N.J.

2/22500

INFILTRATION AND BLOCK ANALGESIA

"minimum of 5 hours' operating time"[1,2]

"postoperative analgesia from 4 to 9 hours"[2]

In a very large series of operative procedures (3000 and 2500 cases, respectively), Bonica[1,3,4] and Moore[2,5] found Pontocaine highly satisfactory for regional anesthesia in virtually all types of operations.

The very low, effective concentrations—0.1 to 0.2 per cent—of Pontocaine hydrochloride account for its high degree of comparative safety.[3]

With Pontocaine "postoperative analgesia is indeed striking and gratifying to the patient, surgeon and anesthesiologist."[2] Prolongation of therapeutic and diagnostic block is another advantage of great importance.

PONTOCAINE®
HYDROCHLORIDE

Supplied

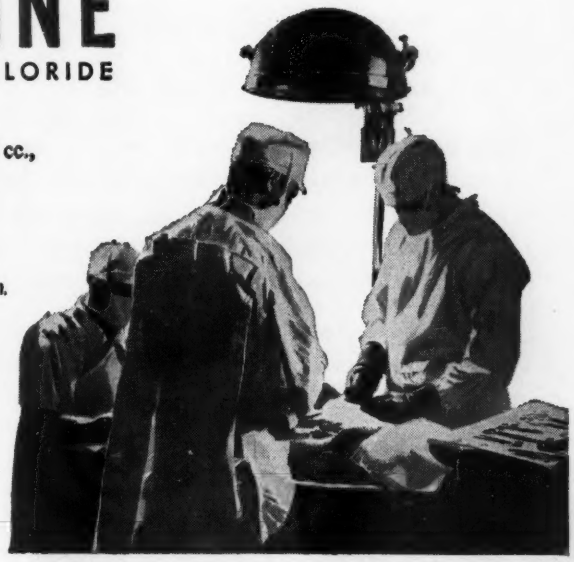
0.15 per cent solution, vials of 100 cc., and instantly soluble "Niphanoid" form in 250 mg. ampuls.

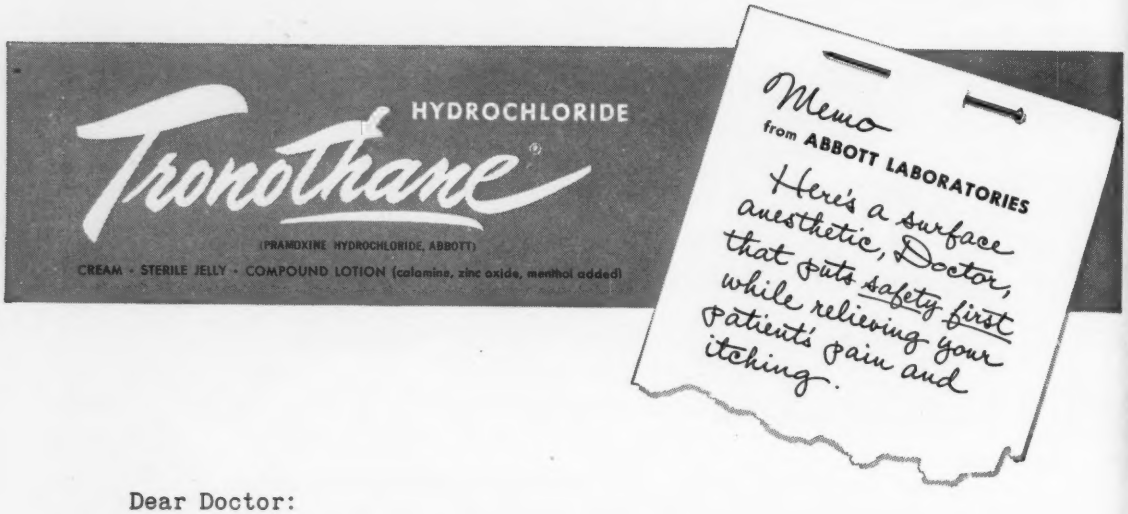
References:

1. Bonica, J. J.: *Anesthesiology*, 11:716, Nov., 1950.
2. Moore, D. C.: *J. A. M. A.*, 146:803, June 30, 1951.
3. Bonica, J. J.: *Anesth. & Analg.*, 30:76, Mar.-Apr., 1951.
4. Bonica, J.J.: The Management of Pain. Philadelphia, Lea & Febiger, Sept., 1953.
5. Moore, D.C.: Regional Block. Springfield, Ill., Charles C. Thomas, 1953.

Pontocaine, trademark reg. U. S. Pat. Off.
brand of tetracaine

Winthrop LABORATORIES
NEW YORK 18, N.Y. • WINDSOR, ONT.





Dear Doctor:

A wide margin of safety is yours when you use Tronothane for surface anesthesia.

For with Tronothane, the incidence of sensitization is so low it is virtually insignificant. You can relieve pain or itching safely even in patients known to be sensitized to other topical agents.

To confirm this unusual freedom from side effects, clinical studies were made of Tronothane's use with more than 15,000 patients. These cases included anogenital pruritus, painful episiotomy, hemorrhoids, rectal surgery, and a wide variety of itching dermatoses, as well as burns and sunburn.

> Not one of these thousands evidenced toxicity. Primary sensitization was negligible. And cross-sensitization was not noted at any time.

Why is Tronothane so well tolerated? The answer is in the formula. Tronothane's chemical structure is in no way related to the agents derived from "caine" drugs. Para-aminobenzoic acids and benzoic acid are not included. Neither are certain chemical groups frequently associated with primary sensitization.

Put it to a test, Doctor, and see if this wide safety margin doesn't expand the usefulness of topical anesthesia in your daily practice.

Sincerely,

Abbott

now

Meti-steroid potency and safety

available for

topical skin therapy

new

Meti-Derm*

Cream 0.5%

with METICORTELONE, original brand of prednisolone

- more active than topical hydrocortisone, milligram for milligram
- no edema and sodium retention reported upon topical administration
- provides topical METICORTELONE in the free alcohol form. For effective relief of allergic (atopic) dermatoses, poison ivy dermatitis and other contact dermatoses, nonspecific anogenital pruritus.

formula: Each gram of METI-DERM Cream contains 5 mg. of prednisolone, free alcohol, in a water-washable base.

also for allergic, inflammatory dermatoses, minor secondary infections

Meti-Derm Ointment with Neomycin

formula: Each gram contains 5 mg. prednisolone and 5 mg. neomycin sulfate (equivalent to 3.5 mg. neomycin base) in a white petrolatum base.

packaging: METI-DERM Cream, 10 Gm. tube.
METI-DERM Ointment, 10 Gm. tube.

METI-DERM,* brand of prednisolone topical.
METICORTELONE,® brand of prednisolone.

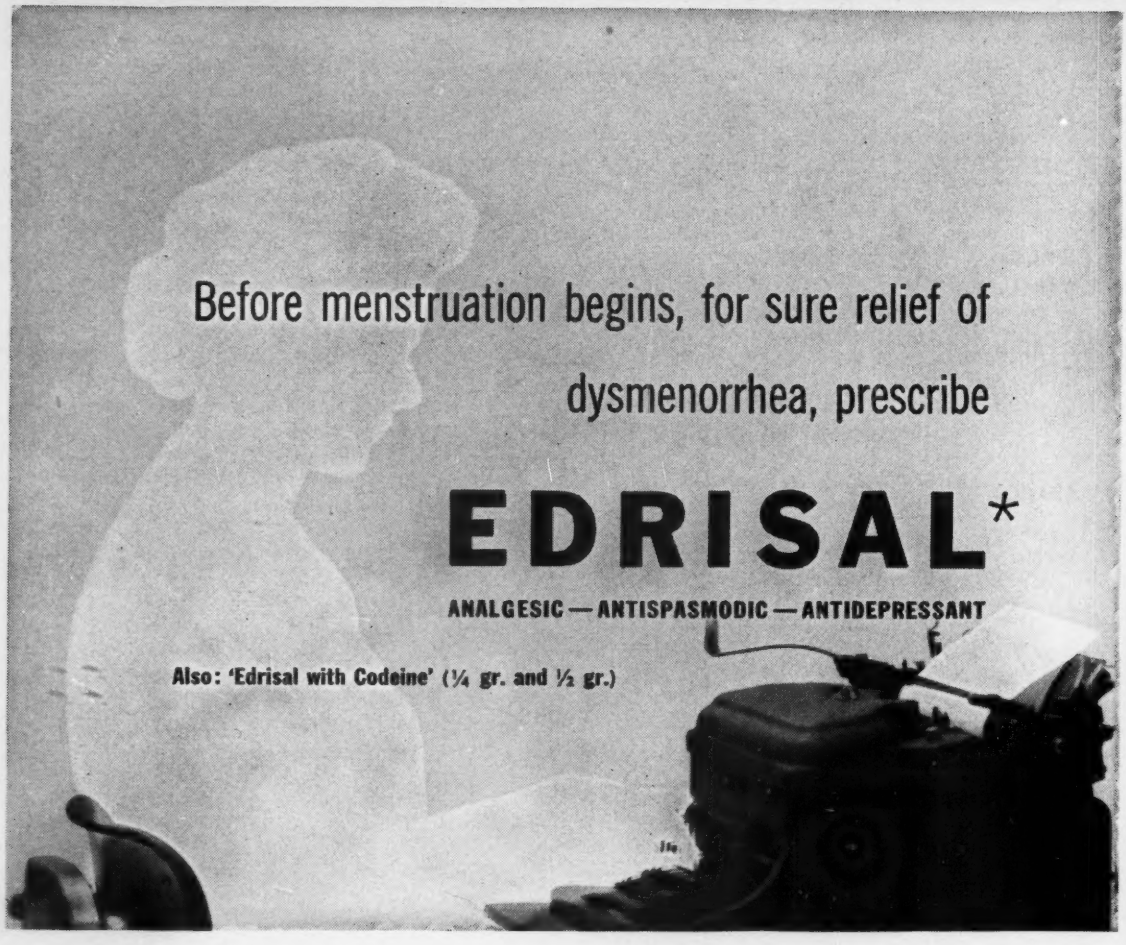
MD-J-356

*T.M.

Schering

"140 million working hours are lost annually as a result of

dysmenorrhea"[1]



two tablets every 3 hours

FORMULA: Each 'Edrisal' tablet contains:

Benzedrine* Sulfate (racemic amphetamine sulfate, S.K.F.)	2.5 mg.
Aspirin	2.5 gr.
Phenacetin	2.5 gr.

1. M. Times 76.416 *T.M. Reg. U.S. Pat. Off.

Smith, Kline & French Laboratories, Philadelphia

to restore
and maintain
vaginal acidity
Aci-jel
Aci-jel®
therapeutic vaginal jelly
Ortho

esthetically acceptable

GENTIAN VIOLET

SUPPRETTES®

SUCCESSOR / TO THE SUPPOSITORY

for treatment of vaginal mycosis.

Gentian Violet Supprettes are preferred by physicians for maximum fungicidal activity . . . by patients for minimal messiness

Gentian Violet Supprettes provide rapid relief from itching, burning, and discharge without irritation to vaginal membranes. Effective even in resistant cases of monilial vaginitis. Messiness and cost are less than with other gentian violet preparations.

Composition: Each Supprette contains gentian violet 0.2%, lactic acid 0.3%, and acetic acid 1.0%.
Supplied: In jars of 12.

- Pregnancy moniliasis
- Antibiotic moniliasis
- Mycotic leukorrhea
- Diabetic vulvitis
- Mycotic vulvovaginitis
- Pruritus vulvae

The "Neocera" Base Makes the Difference

Contains no oils or fatty materials. Consists of water-soluble Carbowaxes* with active dispersal agent. Mixes completely with vaginal and cervical fluids to assure thorough penetration into folds of vaginal wall.

*Trademark U.C.C.

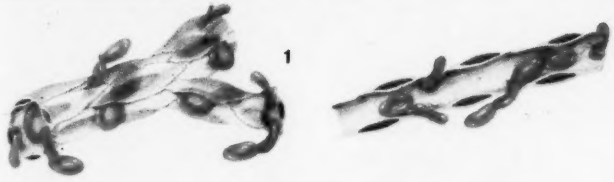
GENTIAN VIOLET SUPPRETTES

NO REFRIGERATION NECESSARY • Samples on Request

Webster **THE WILLIAM A. WEBSTER COMPANY • MEMPHIS 5, TENNESSEE**

95% FETAL SALVAGE

with HESPER-C



1 Red blood cells escaping from a capillary under abnormal conditions of capillary fragility.

2 Bleeding into the decidua basalis results from increased permeability of the uterine capillaries. The decidua then splits; a decidual hematoma is formed which leads to premature separation of the normally implanted placenta.

HESPER-C

makes the difference

the original synergistic nutritional supplement for capillary fragility, is recommended as an integral part of any regimen for fetal salvage.[1] Maintaining capillary integrity during the critical months guards against abruptio placentae.[2] In 100 patients whose 420 previous pregnancies resulted in 95% fetal wastage, the addition of HESPER-C to current therapy completely reversed the figure and resulted in 95% fetal salvage.[3]

Remember Rx HESPER-C along with your usual therapy—it makes the difference.

Maintain the integrity of the capillaries throughout pregnancy.

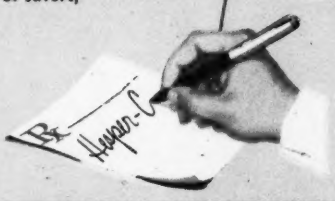
on your prescription only

Now available, convenient New HESPER-C LIQUID.

HESPER-C provides hesperidin concentrate, 100 mg., and ascorbic acid, 100 mg., per capsule and per teaspoonful (5 ml.). DOSAGE: 6 capsules or teaspoonfuls or more per day for the first week. Then 4 capsules or teaspoonfuls daily. SUPPLIED: Liquid in bottles of 4 oz. and 12 oz. Capsules in bottles of 100 and 1000.

REFERENCES: 1. Dill, L. V.: Med. Ann. of D. of C., 23:667, 1954. 2. Greenblatt, R. B.: Obst. and Gyn., 2:530, 1953. 3. Javert, C. T.: Obst. and Gyn., 3:420, 1954.

The film "CLINICAL ENZYMOLOGY" is now available for showing at medical meetings upon your request. And be sure to watch for the MED-AUDIOGRAPHS, a series of recorded clinical discussions.



PRODUCTS OF ORIGINAL RESEARCH

NATIONAL NATIONAL NATIONAL NATIONAL NATIONAL NATIONAL

THE NATIONAL DRUG COMPANY PHILADELPHIA 44, PA.

The CLASSICAL *Vaginal Therapeutic*

UNIQUE WITH 9-AMINOACRIDINE,

the nonirritating, broad-spectrum, stable bactericidal agent. Effective where organisms have become resistant to other drugs.

AVC Improved **has been accepted, and in ever-expanding use for over 12 years, as the most comprehensive therapy in:**

Trichomonal Leukorrheas • Monilial and Nonspecific Vaginitis • Cervicitis • Postpartum Hygiene • Pre- and Postcauterization, Coagulation, Conization and other Vaginal Surgery

AVC Improved **provides: Broad-spectrum, sustained vaginal pathogen killing power because the remarkable synergism of 9-aminoacridine and sulfanilamide effects the actual destruction of the inhibitors of maximum bactericidal action. Surface-active, spreading, penetrating agent; buffered vaginal pH; nutrient for normal vaginal flora; mucus digestion; immediate relief of odor and itching; restoration of vaginal mucosa, by actively promoting tissue repair and granulation.**

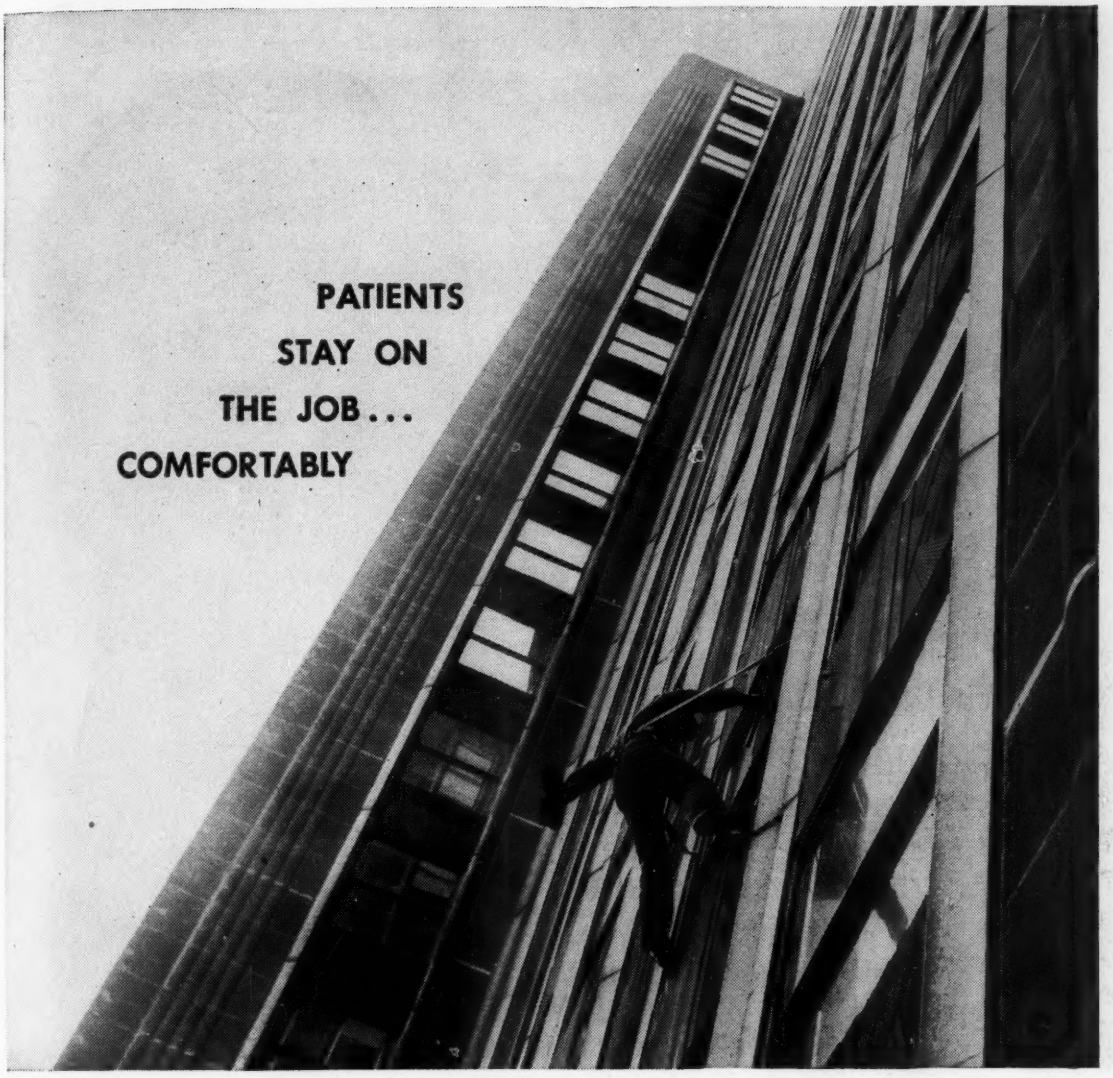
AVC Improved is a cream containing 0.2% 9-Aminoacridine Hydrochloride, 15% Sulfanilamide, 2% Allantoin, in a water-miscible base buffered to approximately pH 4.5.

SUPPLIED: 4 oz. tubes with or without applicator. ADMINISTRATION: An applicatorful of AVC Improved should be introduced high in the vagina twice daily, upon arising and at bedtime.

PRODUCTS OF ORIGINAL RESEARCH

NATIONAL NATIONAL NATIONAL NATIONAL NATIONAL NATIONAL

THE NATIONAL DRUG COMPANY PHILADELPHIA 44, PA.



in URINARY DISTRESS

Pyridium®

(Brand of Phenylazo-diamino-pyridine HCl)

provides gratifying relief in a matter of minutes

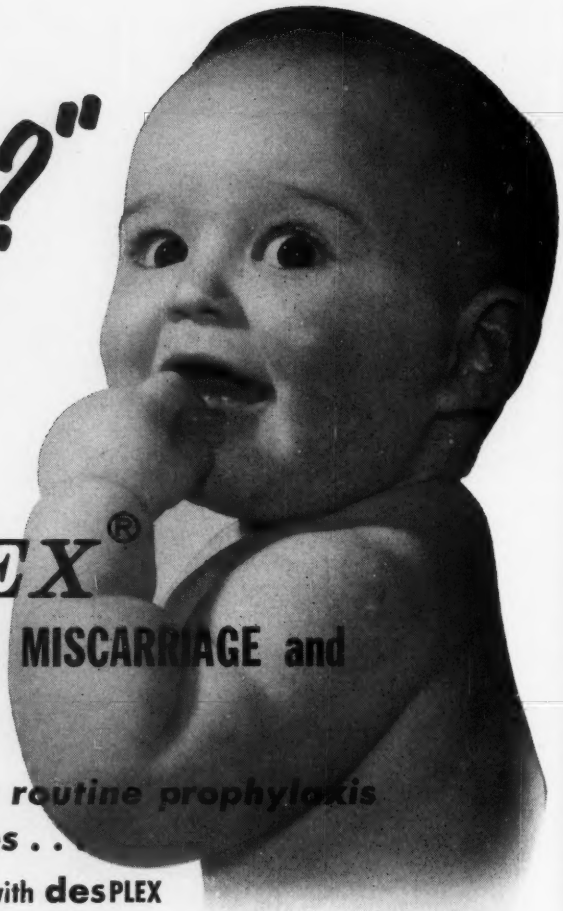
Painful symptoms impel the patient with acute or chronic pyelonephritis, cystitis, urethritis or prostatitis to seek your aid. In the interval before antibiotics, sulfonamides or other antibacterial measures can become effective, the nontoxic, compatible, analgesic action of PYRIDIUM brings prompt relief from urgency, frequency, dysuria, nocturia or spasm. At the same time, PYRIDIUM imparts an orange-red color to the urine which reassures the patient. Used alone or in combination with antibacterial agents, PYRIDIUM may be readily adjusted to each patient by individualized dosage of the total therapy.

SUPPLIED: In 0.1 Gm. (1½ gr.) tablets in vials of 12 and bottles of 50, 500, and 1,000.

PYRIDIUM is the registered trade-mark of Nepera Chemical Co., Inc., for its brand of phenylazo-diamino-pyridine HCl. Sharp & Dohme, Division of Merck & Co., Inc., sole distributor in the United States.

SHARP & DOHME
Philadelphia 1, Pa.
Division of Merck & Co., INC.

"Really?"



Yes...

desPLEX®

to prevent ABORTION, MISCARRIAGE and PREMATURE LABOR

recommended for routine prophylaxis in ALL pregnancies . .

96 per cent live delivery with desPLEX in one series of 1200 patients[4]— — bigger and stronger babies, too.[cf. 1]

No gastric or other side effects with desPLEX — in either high or low dosage[3,4,5]

(Each **des**PLEX tablet starts with 25 mg. of diethylstilbestrol, U.S.P., which is then ultramicronized to smooth and accelerate absorption and activity. A portion of this ultramicronized diethylstilbestrol is even included in the tablet coating *to assure prompt help in emergencies.* **des**PLEX tablets also contain vitamin C and certain members of the vitamin B complex to aid detoxification in pregnancy and the effectuation of estrogen.)

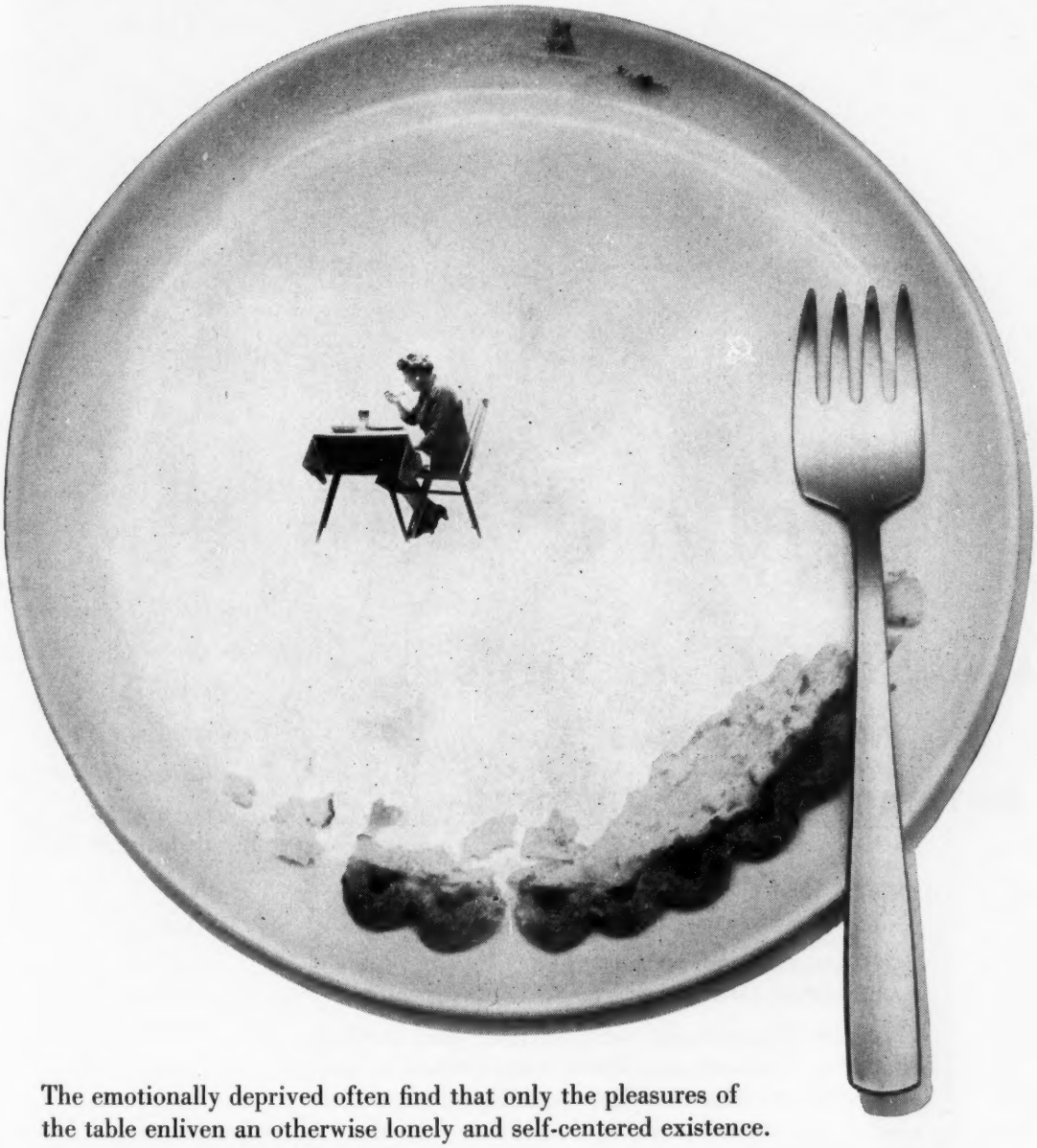
For further data and a generous trial supply of **des**PLEX, write to:
Medical Director

REFERENCES

1. Canario, E. M., et al.: Am. J. Obst. & Gynec. 65:1298, 1953.
2. Gitman, L., and Koplowitz, A.: N. Y. St. J. Med. 50:2823, 1950.
3. Karnaky, K. J.: South. M. J. 45:1166, 1952.
4. Peña, E. F.: Med. Times 82:921, 1954; Am. J. Surg. 87:95, 1954.
5. Ross, J. W.: J. Nat. M. A. 43:20, 1951; 45:223, 1953.

GRANT CHEMICAL COMPANY, INC., Brooklyn 26, N.Y.

for the **overeating** *of the emotionally deprived...*



The emotionally deprived often find that only the pleasures of the table enliven an otherwise lonely and self-centered existence.

'Dexamyl' can help you to relieve—smoothly and subtly—your obese patients' almost compulsive desire to nibble and overeat; it can also help you to encourage those who are lonely and discontent to seek fresh, healthy interests and satisfactions.

Dexamyl* *tablets • elixir • Spansule† capsules*

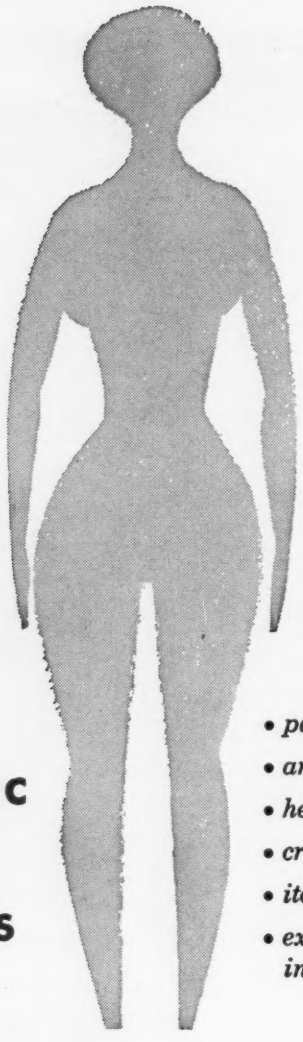
(Dexedrine‡ plus amobarbital)

Smith, Kline & French Laboratories, Philadelphia (SKF)

*T.M. Reg. U.S. Pat. Off.
†T.M. Reg. U.S. Pat. Off. for sustained release capsules, S.K.F.
‡T.M. Reg. U.S. Pat. Off. for dextro-amphetamine sulfate, S.K.F.

Dyclone™

A NEW TOPICAL ANESTHETIC WITH UNIQUE ANTIBACTERIAL PROPERTIES



- *painful stitches*
- *anogenital pruritus*
- *hemorrhoids*
- *cracked nipples*
- *itching dermatoses*
- *examinations and instrumentations*

DOES WHAT A GOOD TOPICAL ANESTHETIC SHOULD DO...

Dyclone brings rapid relief of pain and itching. Moreover, it shows significant antimicrobial properties...with a phenol coefficient of 3.6.

WITHOUT DOING WHAT YOU'RE AFRAID A TOPICAL ANESTHETIC MIGHT DO

Dyclone rarely irritates mucous membranes, and clinical reports on more than 5,000 cases show an insignificant incidence of sensitivity...less than 1/10 of 1%.

Dyclone (dyclonine HCl), is an organic ketone synthesized by Pitman-Moore. It is not a "caine" type compound.

May our Professional Service Department send you reprints of clinical and laboratory reports?

Dyclone Creme, tubes of 1 oz., with rectal applicator. Dyclone Solution, bottles of 1 and 8 oz.

PITMAN-MOORE COMPANY • *Division of Allied Laboratories, Inc.* • **Indianapolis 6, Indiana**

"... may be unique as a wide-spectrum antimicrobial agent that is bactericidal, relatively nontoxic, and does not invoke resistant mutants."[1]

Furadantin®

BRAND OF NITROFURANTOIN

in acute and chronic pyelonephritis, cystitis, prostatitis

Percentage of Effectiveness of Furadantin Against Various Strains of Bacteria in Vitro

	Aerobacter aerogenes	Proteus sp.	Paracolobactrum sp.	Micrococcus pyogenes	Streptococcus pyogenes	Escherichia coli	Pseudomonas aeruginosa
Furadantin	**82.1**	**66.6**	**31.2**	**91.9**	**93.9**	**60.0**	**13.3**
Antibiotic A	71.4	55.5	25.0	93.5	96.9	66.0	26.6
Dihydrostreptomycin	14.2	25.9	12.5	38.7	27.2	28.0	6.6
Antibiotic B	3.5	0	0	66.1	63.6	0	2.2
Penicillin	3.5	0	0	27.4	39.3	0	0
Antibiotic C	14.2	7.4	18.7	46.7	72.6	22.0	11.1

ADAPTED FROM PERRY[2]

Furadantin's "high degree of effectiveness against bacteria responsible for urinary tract infections is brought out by this study."[2]

Furadantin dosage—simple and safe: Average adult dose is 100 mg., q.i.d., (at mealtime, and on retiring, with food or milk). Average daily dosage for children is 5 to 7 mg./Kg. in four divided doses.

SUPPLIED: Tablets, 50 and 100 mg., bottles of 25 and 100.
Oral Suspension, 5 mg. per cc., bottle of 118 cc.

REFERENCES: 1. Waisbren, B. A., and Crowley, W.: A.M.A. Arch. Int. M. 95:653, 1955. 2. Perry, R. E., Jr.: North Carolina M. J. 16:567, 1955.

NITROFURANS—A NEW CLASS OF ANTIMICROBIALS—NEITHER ANTIBIOTICS NOR SULFAS

Eaton LABORATORIES

new

a measurable gain in weight loss

PRELUDIN

(brand of phenmetrazine hydrochloride)

...reduces risk in reducing

By any standard of measurement PRELUDIN...a new, safe, and different anorexiant...constitutes a valuable contribution to the treatment of obesity.

In exhaustive clinical trials PRELUDIN has achieved an outstanding record in safely securing steady, progressive weight loss with virtually complete avoidance of side actions.

Chemically Distinctive: PRELUDIN is a totally new compound of the oxazine series.

Of Proven Effectiveness: PRELUDIN produces significant and progressive weight loss by voluntary effortless restriction of caloric intake.

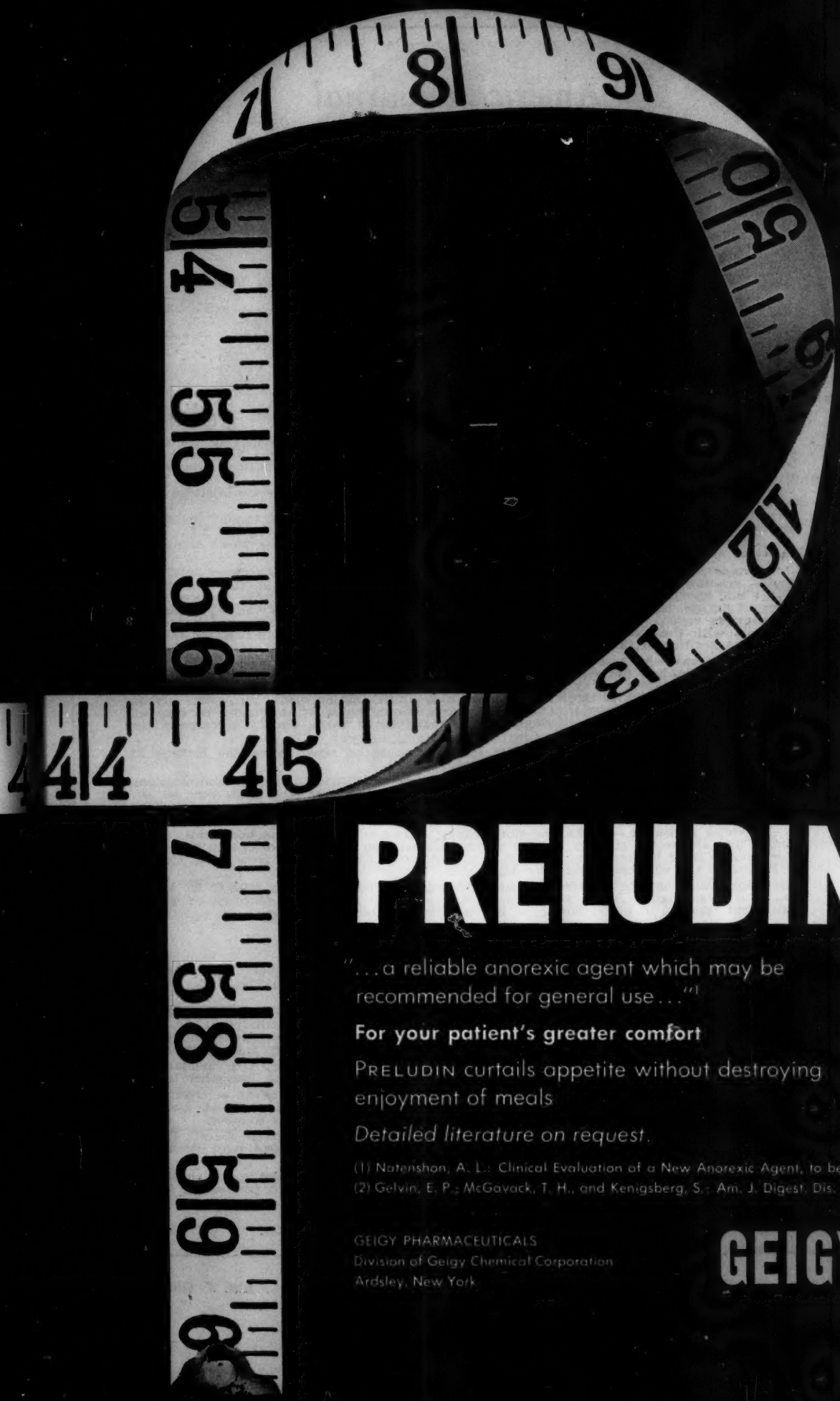
Exceptionally Well Tolerated: With PRELUDIN there is a notable absence of palpitations or nervous excitement.[1,2] PRELUDIN may generally be administered with safety to hypertensive or diabetic patients.

Recommended Dosage: One tablet two to three times daily taken one hour before meals. Occasionally smaller dosage suffices.

PRELUDIN® (brand of phenmetrazine hydrochloride).
Scored square pink tablets of 25 mg. Under license from C. H. Boehringer Sohn, Ingelheim.

Geigy

11554



PRELUDIN

"...a reliable anorexic agent which may be recommended for general use..."[1]

For your patient's greater comfort

PRELUDIN curtails appetite without destroying enjoyment of meals

Detailed literature on request.

(1) Natenshon, A. L.: Clinical Evaluation of a New Anorexic Agent, to be published.
(2) Gelvin, E. P.; McGavack, T. H., and Kenigsberg, S.: Am. J. Digest. Dis. 1: 155, 1956.

GEIGY PHARMACEUTICALS
Division of Geigy Chemical Corporation
Ardsley, New York

GEIGY

American Journal of Obstetrics and Gynecology

Editors: HOWARD C. TAYLOR, JR. AND WILLIAM J. DIECKMANN
622 West 168th St., New York 32, N. Y. 5841 Maryland Ave., Chicago 37, Ill.

PUBLISHED BY THE C. V. MOSBY COMPANY, 3207 WASHINGTON BLVD.
ST. LOUIS 3, MO.

Entered at the Post Office at St. Louis, Mo., as Second-Class Matter.

Published Monthly. Subscriptions may begin at any time.

Editorial Communications

Original Contributions.—Contributions, letters, and all other communications relating to the editorial management of the Journal should be sent to Dr. Howard C. Taylor, Jr., 622 West 168th St., New York 32, N. Y., or to Dr. William J. Dieckmann, 5841 Maryland Ave., Chicago 37, Ill.

All articles published in this Journal must be contributed to it exclusively. If subsequently printed elsewhere (except in a volume of Society Transactions) due credit shall be given for original publication. The Editors rely on all contributions conforming strictly to this rule.

Members of the Advisory Editorial Board may be consulted by the Editors upon suitability of papers submitted for publication.

It is assumed by the Editors that articles emanating from a particular institution are submitted with the approval of the requisite authority.

Neither the Editors nor the publishers accept responsibility for the views and statements of authors as published in their "Original Communications."

Manuscripts.—Manuscripts should be typewritten on one side of the paper only, with double spacing and liberal margins. References should be placed at the end of the article and should conform to the style of the Quarterly Cumulative Index Medicus: viz., name of author, name of periodical, volume, page, and year. Illustrations accompanying manuscripts should be numbered, provided with suitable legends, and marked lightly on the back with the author's name. Authors should indicate on the manuscript the approximate position of tables and text figures.

Illustrations.—A reasonable number of halftone illustrations will be reproduced free of cost to the author, but special arrangements must be made with the editors for color plates, elaborate tables, or extra illustrations. Copy for zinc cuts (such as pen drawings and charts) must be drawn and lettered in India ink or black typewriter ribbon (when the typewriter is used). Only good glossy photographic prints should be supplied for halftone work; original drawings, not photographs of them, should accompany the manuscript.

Announcements.—Announcements of meetings must be received by the Editors at least 2½ months before the time of the meeting.

Exchanges.—Contributions, letters, exchanges, reprints, and all other communications relating to the Abstract or Review Department of the Journal should be sent to Dr. Louis M. Hellman, State University of New York, College of Medicine, 451 Clarkson Ave., Brooklyn 3, N. Y.

Reviews of Books.—Books and monographs, native and foreign, on obstetrics, gynecology, and abdominal surgery will be reviewed according to their merits and the space at disposal. Send books to Dr. Louis M. Hellman, State University of New York, College of Medicine, 451 Clarkson Ave., Brooklyn 3, N. Y.

Reprints.—Reprints of articles must be ordered from the publishers, The C. V. Mosby Co., 3207 Washington Blvd., St. Louis 3, Mo., who will send their schedule of prices. Individual reprints of an article must be obtained through the author.

Business Communications

Business Communications.—All communications in regard to advertising, subscriptions, changes of address, etc., should be addressed to the publishers, The C. V. Mosby Co., 3207 Washington Blvd., St. Louis 3, Mo.

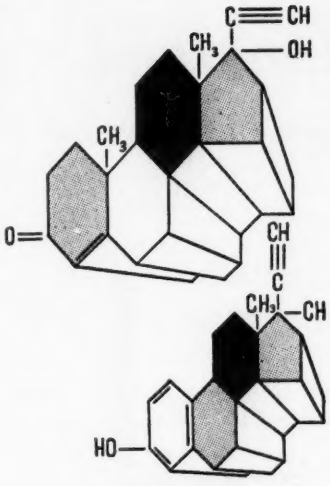
Subscription Rates.—United States and its Possessions $15.00, Students $7.50; Canada, Latin-America, and Spain $16.00, Students $8.50; Other Countries $17.50, Students $10.00. Single copies, $2.50 postpaid. Remittances for subscriptions should be made by check, draft, post office or express money order, payable to this Journal.

Publication Order.—The monthly issues of this Journal form two semiannual volumes; the index is in the last issue of the volume—in the June and December issues.

Change of Address Notice.—Six weeks' notice is required to effect a change of address. Kindly give the exact name under which a subscription is entered, and the full form of both old and new addresses, including the post office zone number.

Advertisements.—Only products of known scientific value will be given space. Forms close first day of month preceding date of issue. Advertising rates and page sizes will be given on application.

Bound Volumes.—Publishers' Authorized Bindery Service, 308 West Randolph Street, Chicago 6, Illinois, will quote prices for binding complete volumes in permanent buckram.



to regulate the menstrual cycle

"do as the ovaries do"

Duosterone®

anhydrohydroxyprogesterone 10.00 mg.
primed by ethinyl estradiol 0.01 mg.
} per tablet

a physiologic regulator

For *Simplified, Oral Treatment* of *Secondary Amenorrhea:* infrequent periods, subnormal flow, *Dysfunctional Uterine Bleeding:* menorrhagia, relapse after curettage, irregular or too frequent periods, prolonged or profuse menses.

other indications

Habitual abortion, threatened abortion, functional sterility, dysmenorrhea, and premenstrual tension have responded to DUOSTERONE therapy.

action

DUOSTERONE simulates the normal ovarian endocrine pattern of the secretory phase of the menstrual cycle. A normal cycle may be set off by DUOSTERONE stimulation, much as touching the pendulum starts a wound clock. Normal menstrual function is *safely* and conveniently restored with essential, two-hormone action provided by DUOSTERONE: (1) Administration of needed progesterone, and (2) Estrogen priming, which is indispensable to adequate progesterone activity.

DUOSTERONE may also initiate an endocrine chain-reaction resulting in spontaneous ovulatory cycles according to the concept of Holmstrom.*

dosage

5 to 10 tablets per day for five days, beginning exactly one week before expected onset of menses. No medication is given on last two days. Repeat dosage for six successive cycles to ensure reestablishment of normal function.

supplied

Bottles of 25 and 100 tablets. On prescription only.

*Am. J. Obst. & Gynec., 68:1321, 1954.

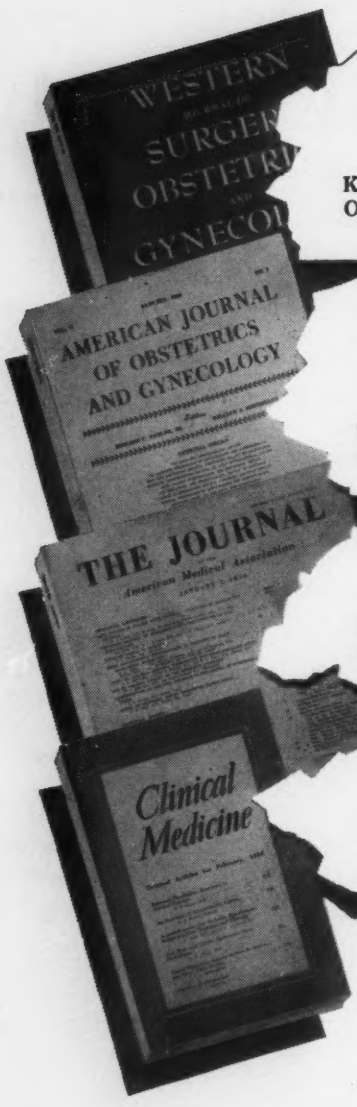
ROUSSEL

ROUSSEL CORPORATION • 155 East 44th St., New York 17, N.Y.

Small diameter, ESTRONE PELLETS, ROUSSEL, 50 mg., for subcutaneous injection of pure, crystalline estrone to relieve menopausal symptoms for 3 months, according to the technique of TeLinde.[1] (Johns Hopkins Hospital.) Write for literature. (1.) TeLinde, R. W., Operative Gynecology, 2nd Ed., J. B. Lippincott Co., Philadelphia, 1953.

TAMPAX

a clinically accepted method of menstrual hygiene



"Free from harm or irritation to the vaginal and cervical mucosa."

Karnaky, K. J.: Western Journal of Surgery, Obstetrics and Gynecology, Vol. 51, pp. 150-152.

"No evidence that the use of the tampon caused obstruction to menstrual flow."

Thornton, M. J.: American Journal of Obstetrics and Gynecology, Vol. 46, pp. 259-265.

"Does not impair standard anatomic virginity."

Dickinson, R. L.: The Journal of the American Medical Association, Vol. 128, pp. 490-494.

"Easy and comfortable to use and eliminated odor."

Sackren, H. S.: Clinical Medicine, Vol. 46, pp. 327-329.

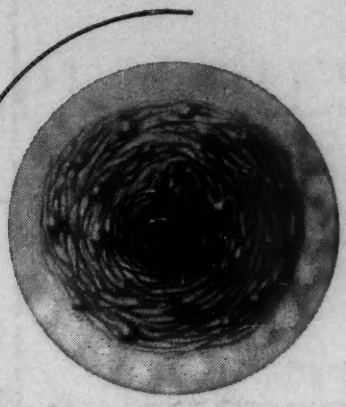
OB-6-6

Three absorbencies: Junior, Regular, or Super Tampax meet varying requirements.

TAMPAX

Professional samples and reprints of these papers furnished on request.

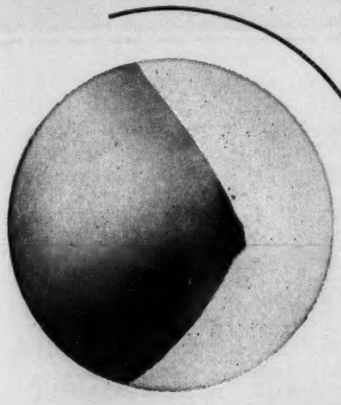
Tampax Incorporated, Palmer, Massachusetts



FISSURED NIPPLE THERAPY

The use of White's Vitamin A & D Ointment soothes and softens the fissured nipple, promotes tissue regeneration.

WHITE'S VITAMIN A & D OINTMENT

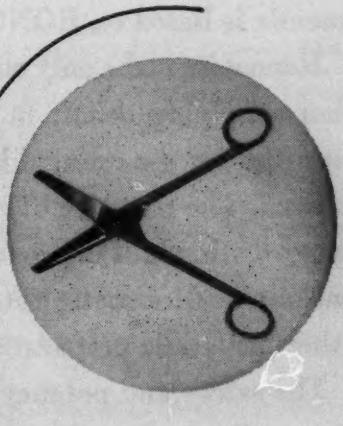


NIPPLE ROUTINE

—a valuable and simple prophylactic measure against drying, fissuring and erosion.

AFTER EPISIOTOMIES

As a post-surgical dressing, White's Vitamin A & D Ointment provides comfort for the patient and encourages rapid healing.

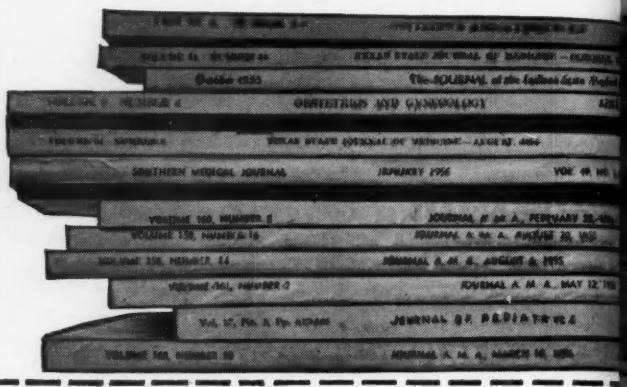


Specify White's Vitamin A & D Ointment also in such conditions as burns, diaper rash, chafing, indolent ulcers.
Recommend the 1½ or 4 oz. tubes; the 1 lb. or 5 lb. jars.

White's

WHITE LABORATORIES, INC./KENILWORTH, NEW JERSEY

"...THE MOST EFFECTIVE HEMATINIC..."*



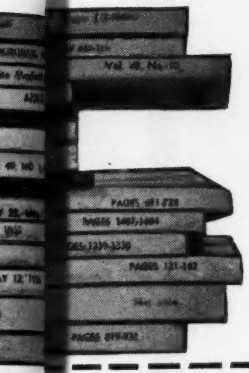
The convincing evidence supporting the unique and advanced concept of cobalt-iron therapy in anemia is based on RONCOVITE research.

Roncovite is the only clinically proved preparation supplying cobalt in the therapeutic levels essential for the optimal hematologic response in anemia. The presence of cobalt as a specific bone marrow stimulant improves the utilization of iron and makes Roncovite totally different from any other hematinic preparation.

The safety and potency of Roncovite has been repeatedly confirmed.

Your own results will show why "The bibliography specifies RONCOVITE."

BIBLIOGRAPHY SPECIFIES



RONCOVITE®

—THE ORIGINAL CLINICALLY PROVED COBALT-IRON PRODUCT—

Holly, R.G.: Anemia in Pregnancy, Obst. & Gynec. **5**:562 (April) 1955.

Hill, J.M., et al.: Cobalt Therapy in Anemia, Texas J. Med. **51**:686 (Oct.) 1955.

Rohn, R.J.; Bond, W.H., and Klotz, L.J.: The Effect of Cobalt-Iron Therapy in Iron-Deficiency Anemia in Infants, J. Indiana M.A. **46**: 1253 (1953).

Holly, R.G.: Anemia in Pregnancy, Paper delivered before Amer. Congress of Obstetrics and Gynecology (Dec.) 1954.

* Holly, R.G.: The Value of Iron Therapy in Pregnancy, Journal Lancet **74**:211 (June) 1954.

Quilligan, J.J., Jr.: Effect of a Cobalt-Iron Mixture on the Anemia of Prematurity, Texas J. Med. **50**: 294 (May) 1954.

Hamilton, H.G.: The Use of Cobalt and Iron in the Prevention of Anemia of Pregnancy. Paper delivered before the South. Med. Assn.

Rohn, R.J., and Bond, W.H.: Observations on Some Hematological Effects of Cobalt-Iron Mixtures, Journal Lancet **73**:317 (Aug.) 1953.

Holly, R.G.: Studies on Iron and Cobalt Metabolism, J.A.M.A. **158**: 1349 (Aug.13) 1955.

Jaimet, C.H., and Thode, H.G.: Thyroid Function Studies on Children Receiving Cobalt Therapy, J.A.M.A. **158**:1353 (Aug. 13) 1955.

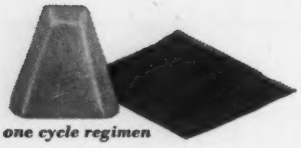
Klinck, G.H.: Thyroid Hyperplasia in Young Children, J.A.M.A. **158**:1347 (Aug. 13) 1955.

Tevetoglu, F.: The Treatment of Common Anemias in Infancy and Childhood with a Cobalt-Iron Mixture, J. Pediat. **49**:46 (July) 1956.

Ausman, D.C.: Cobalt-Iron Therapy in the Treatment of Some Common Anemias Seen in General Practice, in press.

LLOYD BROTHERS, INC.

Cincinnati 3, Ohio



one cycle regimen

Vaginal trichomoniasis: lasting cure for 93.8%

Within 72 hours, local irritation no longer troubled this patient. Relief resulted from thorough powder insufflation by her doctor and her use of suppositories at home.

- after clinical study of 48 active cases, Schwartz reported 93.8% were symptom-free in 3 days; 97.9% showed no motile trichomonads on smear in 7 days; 93.8% had no recurrence 1 to 3 months after treatment through one menstrual cycle*
- advantages: contains a specific, trichomonacidal nitrofuran. Kills many secondary invaders but permits Döderlein's bacillus to exist. Effective in blood, pus and vaginal debris
- office treatment: insufflate TRICOFURON Vaginal Powder twice the first week and once a week thereafter
- home treatment: first week—the patient inserts one TRICOFURON Vaginal Suppository each morning and one each night at bedtime. Thereafter: one a day—a second if needed—to maintain trichomonacidal action

TRICOFURON T. M.

EATON LABORATORIES
Norwich New York

NITROFURANS
a *new* class of antimicrobials
neither antibiotics nor sulfonamides

VAGINAL SUPPOSITORIES AND POWDER

Suppositories: 0.25% Furoxone® (brand of furazolidone) in a water-miscible base of Carbowax and 20 dendro palmitic acid. Sealed in green foil, box of 12.

Powder: 0.1% Furoxone in an acidic powder base of lactose, dextrose, citric acid and a silicate. Bottle of 30 Gm.

*Schwartz, J.: Obst. Gyn. N. Y. 7:312, 1956.

HOMAGENETS®*

The homogenized vitamins

Homagenets supply vitamins in the same way as do the most nutritious foods. In this new dosage form, the vitamins are homogenized, then fused into a solid tablet. Because they are minutely subdivided, the vitamins are absorbed and utilized much more efficiently.

- *Better absorption, better utilization*
- *Excess vitamin dosage unnecessary*
- *Pleasant, candy-like flavor*
- *No regurgitation, no "fishy burp"*
- *May be chewed, swallowed or dissolved in the mouth*

Three formulas: Prenatal, Pediatric, Therapeutic

Samples available on request

*U.S. Pat. 2676136

THE S. E. MASSENGILL COMPANY • Bristol, Tennessee • New York • Kansas City • San Francisco

UROLOGICAL SURGERY

by

AUSTIN INGRAM DODSON, M.D., F.A.C.S.

Richmond, Virginia

3rd (1956) Edition **868 pages, 650 illustrations** **$20.00**

Here is a book covering the entire subject of Urological Surgery. Where improvements in former procedures have been made, they are included. New operations, when considered to advantage, are added. A new chapter on Adrenal Surgery has been added.

Three chapters occurring in the two previous editions have been eliminated. The problem of Acid-Base Balance and Fluid Administration has become too broad a subject to be treated adequately in a single chapter. A brief discussion of this subject as well as Blood Transfusions and the Treatment of Shock is included in the chapter on Preoperative and Postoperative Care. Radiation therapy, with the addition of new radioactive substances, has become too broad a subject to be adequately discussed in the space available. By eliminating these chapters surgical procedures and illustrations have been added.

The chapter on surgical diseases of the adrenal glands and the section on ureterosigmoidostomy, Chapter XXIII, have been rewritten by Dr. A. I. Dodson, Jr. Chapter XXXII in the second edition—Neurogenic Diseases of the Bladder—has been replaced by a chapter on Surgical Treatment of Urinary Tract Dysfunction Caused by Disease or Injury of the Nervous System. This chapter by Dr. Robert C. Bunts deals chiefly with the urological rehabilitation of the paraplegic patient.

The section on Perineal Prostatectomy has been rewritten by Dr. Albert E. Goldstein with new illustrations. In Chapter XXXVI more attention is given the problem of stress incontinence, and operations found beneficial in the author's experience have been added. Some changes have been made in many of the remaining chapters, consisting chiefly in the addition of surgical procedures or illustrations. A separate chapter has been added dealing with postoperative incontinence of the male.

THE C. V. MOSBY COMPANY DATE_____

3207 Washington Blvd., St. Louis 3, Missouri

Gentlemen: Send me the Third (1956) Edition of Dodson "UROLOGICAL SURGERY." Price, $20.00.

DR._____ STREET_____

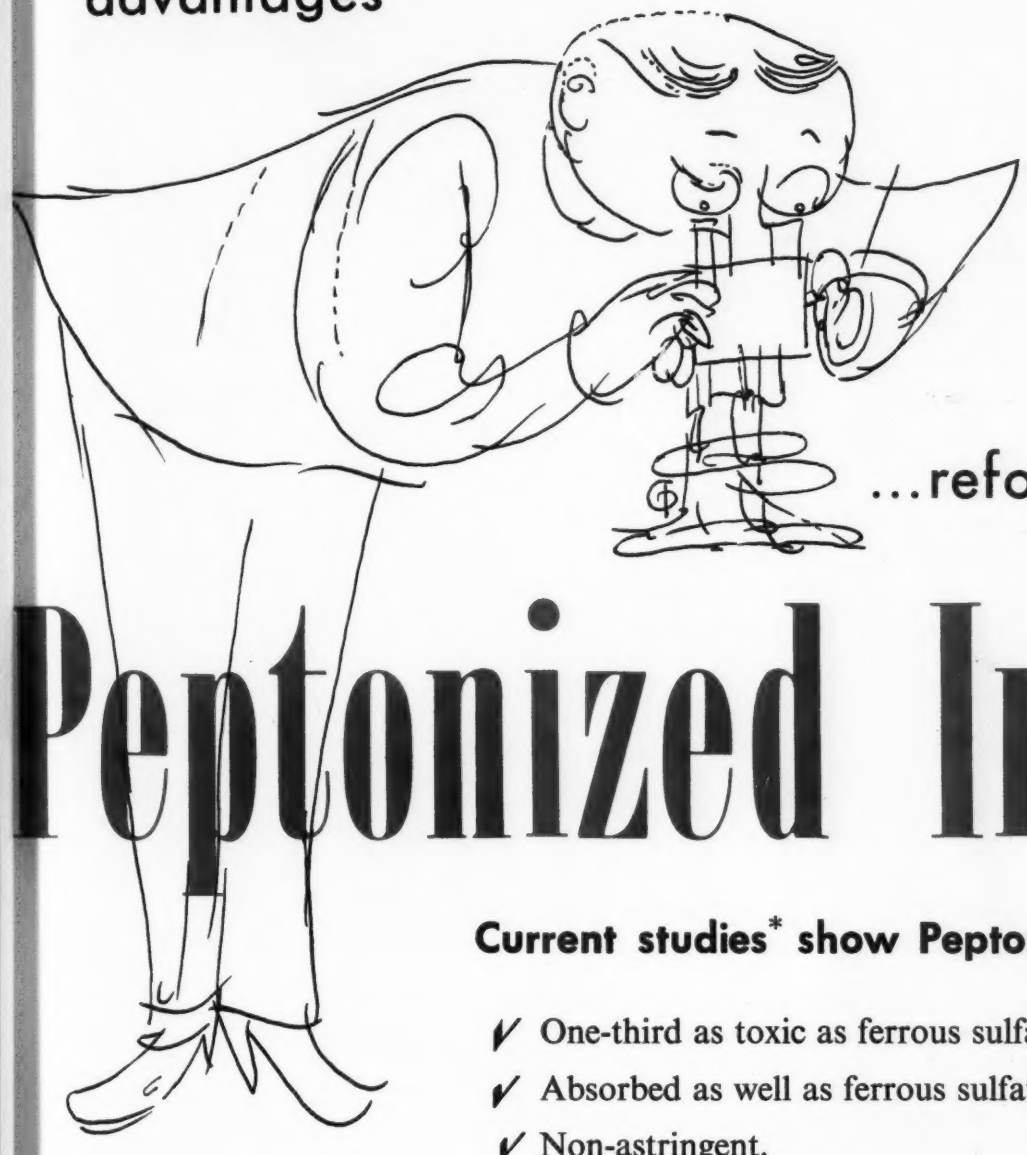
CITY_____ ZONE_____ STATE_____

AJOG—8-56

for assured

herapeutic

advantages



...refocus on...

Peptonized Iron

Current studies* show Peptonized Iron—

- ✓ One-third as toxic as ferrous sulfate.
- ✓ Absorbed as well as ferrous sulfate.
- ✓ Non-astringent.
- ✓ Free from tendencies to disturb digestion. (*One-tenth as irritating to the gastric mucosa as ferrous sulfate.*)
- ✓ More effective in iron-deficient anemias.

LIVITAMIN® with Peptonized Iron

*Keith, J. H.: Utilization and Toxicity of Peptonized Iron and Ferrous Sulfate, Read before the American Association for the Advancement of Science, Zoological Section, Atlanta, Georgia, December, 1955.

THE S. E. MASSENGILL COMPANY Bristol, Tennessee • New York • Kansas City • San Francisco

The preferred hematinic with PEPTONIZED iron

LIVITAMIN

Peptonized iron is virtually predigested. It is absorbed as well as ferrous sulfate, and is one-tenth as irritating to the gastric mucosa. Anemias refractory to other forms of iron will often respond promptly to Livitamin therapy.

The Livitamin formula, containing the B complex, provides integrated therapy to correct the blood picture, and to improve appetite and digestion.

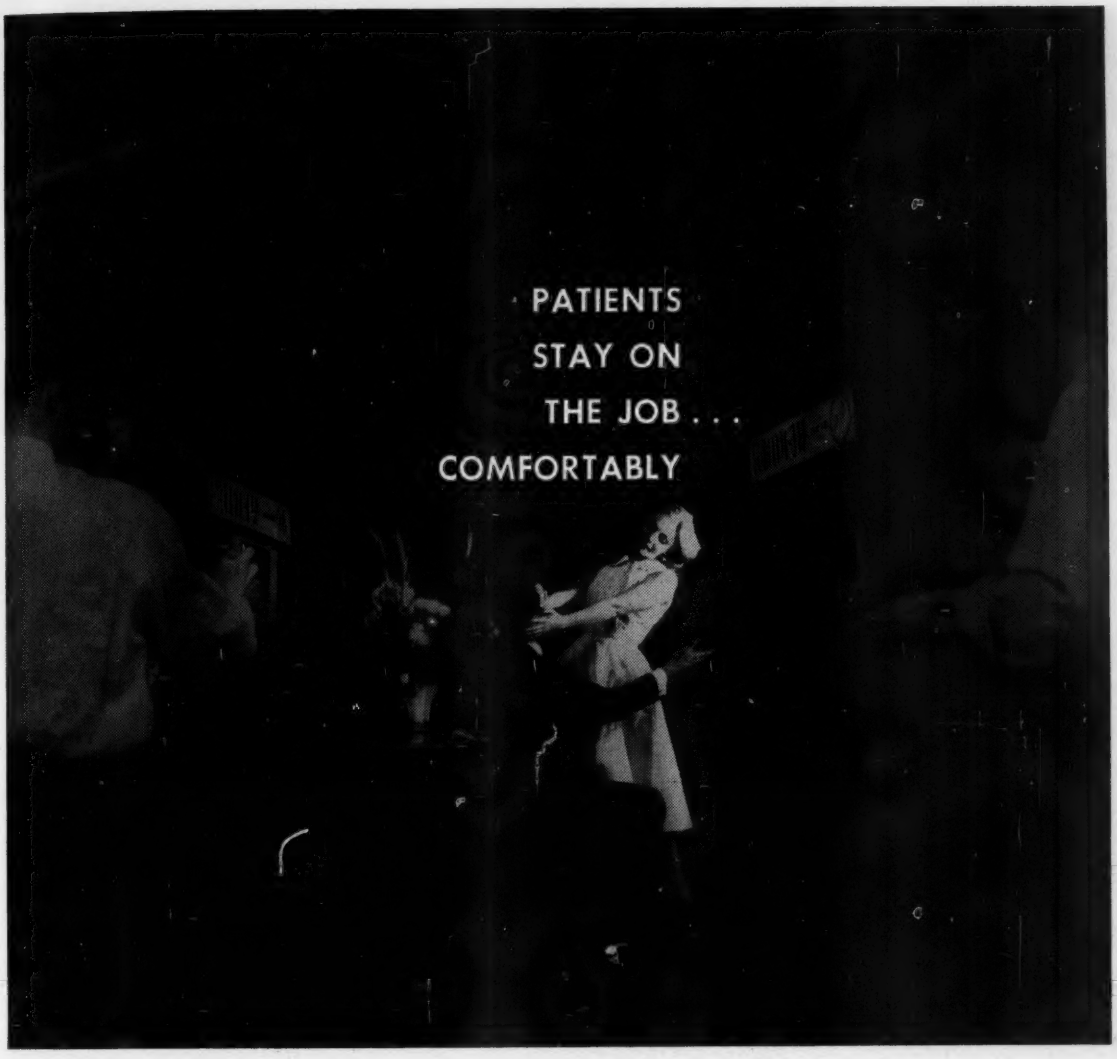
Each fluidounce contains:

Iron peptonized (Equiv. in elemental iron to 71 mg.)	420 mg.
Manganese citrate, soluble	158 mg.
Thiamine hydrochloride	10 mg.
Riboflavin	10 mg.
Vitamin B_{12} (crystalline)	20 mcg.
Niacinamide	50 mg.
Pyridoxine hydrochloride	1 mg.
Pantothenic acid	5 mg.
Liver fraction 1	2 Gm.
Rice bran extract	1 Gm.
Inositol	30 mg.
Choline	60 mg.

THE S. E. MASSENGILL COMPANY

Bristol, Tennessee

New York Kansas City San Francisco



in URINARY DISTRESS

Pyridium®

(Brand of Phenylazo-diamino-pyridine HCl)

provides gratifying relief in a matter of minutes

Painful symptoms impel the patient with acute or chronic pyelonephritis, cystitis, urethritis or prostatitis to seek your aid. In the interval before antibiotics, sulfonamides or other antibacterial measures can become effective, the nontoxic, compatible, analgesic action of PYRIDIUM brings prompt relief from urgency, frequency, dysuria, nocturia or spasm. At the same time, PYRIDIUM imparts an orange-red color to the urine which reassures the patient. Used alone or in combination with antibacterial agents, PYRIDIUM may be readily adjusted to each patient by individualized dosage of the total therapy.

SUPPLIED: In 0.1 Gm. (1½ gr.) tablets in vials of 12 and bottles of 50, 500, and 1,000.

PYRIDIUM is the registered trade-mark of Nepera Chemical Co., Inc., for its brand of phenylazo-diamino-pyridine HCl. Sharp & Dohme, Division of Merck & Co., Inc., sole distributor in the United States.

MERCK SHARP & DOHME
Philadelphia 1, Pa.
Division of MERCK & CO., INC.

NOW!

improved

MEDOPAQUE-H

For Hysterosalpingography

RADIOLOGICALLY SUPERIOR

Increased net iodine content (20%) in the improved Medopaque-H formula provides roentgenograms of superior contrast and diagnostic value. Altered anatomical status is clearly and sharply delineated.

CLINICALLY IMPROVED

Thoroughly miscible, amply viscous, the new Medopaque-H formula is well tolerated. Completely absorbable polyethylene glycols now replace viscous CMC (carboxymethylcellulose).

$1.75 per 10cc. vial. In quantity as low as $1.50.

MEDOPAQUE-H is a sterile, aqueous and viscous solution containing 35% Sodium Ortho-iodohippurate, 10% Sodium Iodide and a blend of polyethylene glycols.

BELL CRAIG, INC. ***Manfacturing Chemists, 270 Lafayette St., New York 12***

American-MacEachern

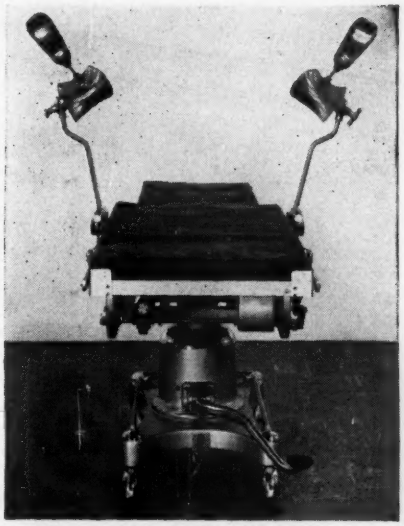
22" Operative Delivery Table.....

FOR ABDOMINAL OR PERINEAL ROUTE DELIVERY

• The new 22" **500N** table assures both the patient and the Obstetrician the fullest advantages of modern obstetrical practice under *all* conditions.

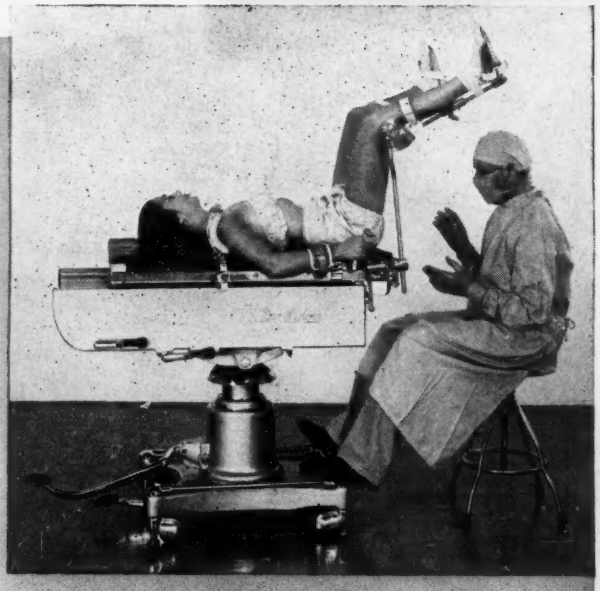
The growing practice of performing cesarian sections in the O. B. room . . . without moving or disturbing the patient . . . is made easy by the 22" surgery width of the **500N.** Yet the table will accommodate even the largest patient during normal delivery and the universally adjustable knee and foot rests accommodate all patients fron the tallest to the shortest.

Write for bulletin C171



The "clean" lines of the 500N table provide maximum comfort and freedom for the surgeon . . . with toe space, folding handles, etc.

If non-elective cesarian section is indicated, patient is quickly and easily positioned for surgery simply by lowering extremities and raising the foot section. The anesthetist need not change position of head of patient.



15" height adjustment and every known obstetrical posture from high lithotomy to Walcher position provides convenient approach to the perineal field.

AMERICAN STERILIZER
Erie • Pennsylvania

BRANCH OFFICES IN 14 PRINCIPAL CITIES

how Pambromal relieves premenstrual tension—

(FROM AN ACTUAL CASE HISTORY)

CASE HISTORY

NAME L.W. AGE 31 y. SEX F. MARITAL STATUS Married

DATE 1/25/55

DIAGNOSIS Alimentary obesity on emotional basis.

COMPLAINTS Obesity. Moderate dysmenorrhea. Premenstrual tension with bloating.

PHYSICAL EXAMINATION Negative.

THERAPY Placed on 1000 calorie diet. D-amphetamine. Thyroid. Pambromal tablets (2 to 3 tabs. a day) to be taken 1 week before menses.

Striking relief from all premenstrual symptoms. Patient stated that it was the first time that she had had any relief from her premenstrual symptoms.

FOLLOW-UP 10/27/55. Lost 35 lbs. No complaints.

WHITTIER LABORATORIES • CHICAGO 11, ILLINOIS Whitti

COMMENT:

The premenstrual tension syndrome, in many instances, is an incidental complaint. The patient often consults the physician for some unrelated disease. In spite of the emotional problems it creates, quite a few patients may forget mentioning their distress unless specifically asked for the symptoms.

Now, relief can be given and it is deeply appreciated...

PAMBROMAL *neutralizes the antidiuretic hormone*

	subject 1	subject 2	subject 3
Diuresis without pamabrom	106 cc.	275 cc.	210 cc.
Diuresis with pamabrom (100 mg.)	950 cc.	980 cc.	1200 cc.

Subjects were given 1000 cc. of water and injected with antidiuretic hormone (pitressin). When pamabrom (an ingredient of Pambromal) was administered, the water-retaining effect of the antidiuretic hormone was almost completely neutralized.

(Bickers, W., and Wood, M.: New England J. Med. 240: 453, 1951)

PAMBROMAL *controls nervous system lability*

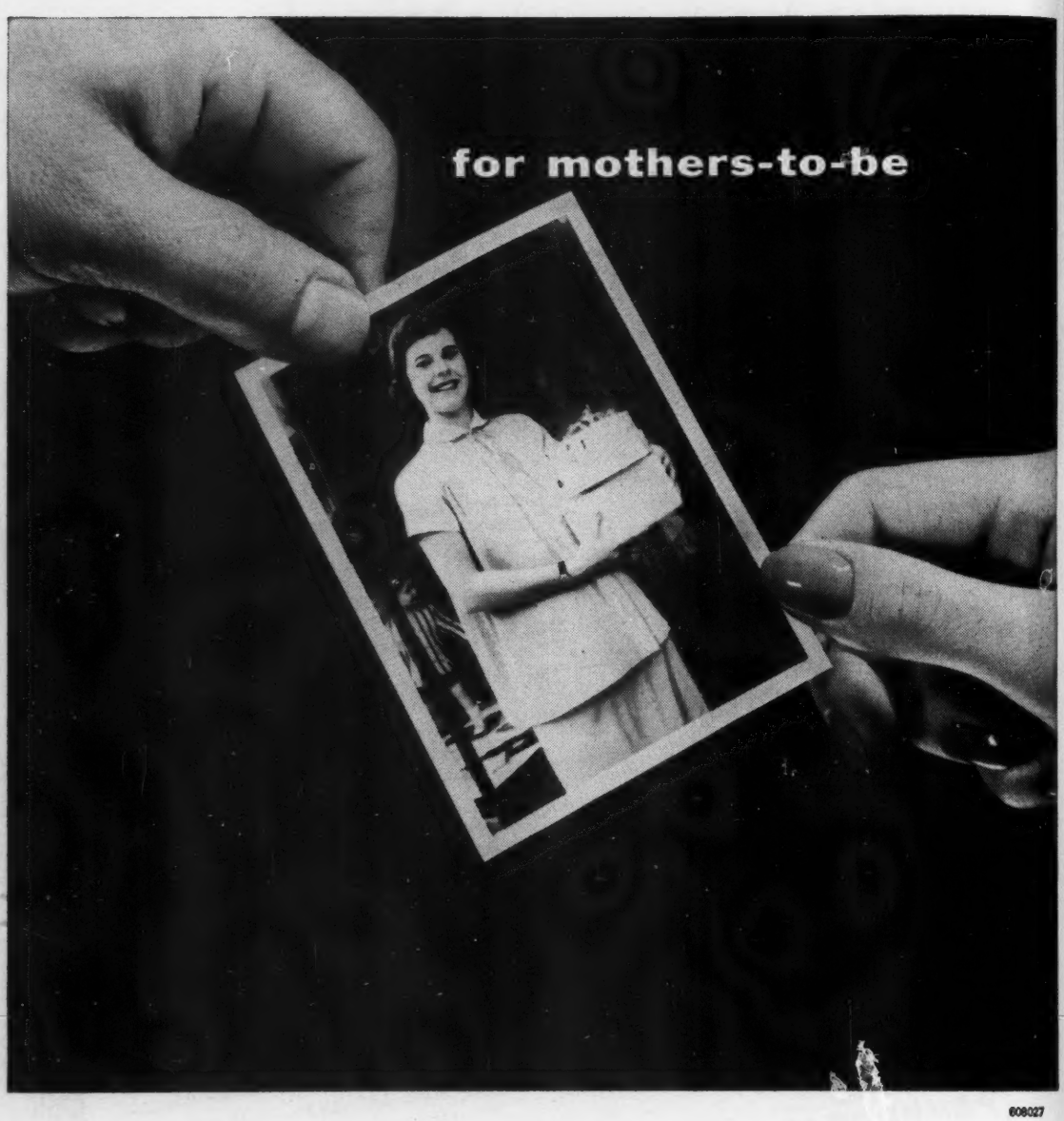
Contains both dextro-amphetamine sulfate and carbromal, a reliable sedative...counteracts irritability, anxiety and fatigue...relaxes tensions.

PAMBROMAL *relieves pain more effectively*

Contains salicylamide—a time-tested and proven analgesic considerably more potent than other salicylates.

Each tablet contains:
Pamabrom (to neutralize the antidiuretic hormone) .....50 mg.
Dextro-amphetamine sulfate (to elevate mood).....2.5 mg.
Carbromal (to relax tension)...130 mg.
Salicylamide (to relieve pain)..250 mg.
Bottles of 24 and 100

PAMBROMAL®
tablets



608027

PRENALAC

(PRENATAL NUTRITIONAL SUPPLEMENTS, LILLY)

helps carry the nutritional burden of pregnancy

'Prenalac' combines essential supplements for better health and fewer nutritional complications during pregnancy and lactation. Two Pulvules 'Prenalac' given three times daily provide the daily vitamin and mineral allowances suggested by the Food and Nutrition Board of the National Research Council.

A DISTINGUISHED MEMBER OF THE *Lilly* FAMILY OF VITAMINS

80TH ANNIVERSARY 1876 · 1956 / ELI LILLY AND COMPANY

American Journal of Obstetrics and Gynecology

VOL. 72 AUGUST, 1956 No. 2

Original Communications

CATHETERIZATION STUDIES OF CARDIAC HEMODYNAMICS IN NORMAL PREGNANT WOMEN WITH REFERENCE TO LEFT VENTRICULAR WORK*†

DAVID J. ROSE,** MORTIMER E. BADER,*** RICHARD A. BADER,*** AND EUGENE BRAUNWALD,**** NEW YORK, N. Y.

(From the Departments of Obstetrics and Gynecology and Medicine, The Mount Sinai Hospital, New York)

MEASUREMENT of the cardiac output and of the pressures in the right heart and pulmonary artery at rest and during exercise throughout normal pregnancy provides the criteria necessary for hemodynamic evaluation of the pregnant patient with heart disease. Such information would be useful not only when considering possible surgical intervention for cardiac lesions, but also in furthering the understanding of the physiology of normal pregnancy and the pathophysiology of heart disease in pregnancy. This has particular application to two practical problems: whether to terminate pregnancy or to permit its continuation, and also whether or not puerperal sterilization is indicated. Apart from surgical considerations, such hemodynamic data provide an index of myocardial function which may be useful in assessing cardiac reserve. While a large body of information has been obtained in recent years regarding hemodynamics in the nonpregnant state in normal subjects and in patients with heart disease, these data cannot be simply transferred and applied to the pregnant woman because of the numerous circulatory alterations which take place during gestation.

*Supported by a Grant (H-1149) from the National Heart Institute of the United States Public Health Service.

†Presented at a meeting of the New York Obstetrical Society, Feb. 7, 1955.

**Charles Klingenstein Fellow.

***Sara Welt Fellow.

****Post Doctoral Research Fellow, National Health Institute, U. S. Public Health Service.

NOTE: The Editors accept no responsibility for the views and statements of authors as published in their "Original Communications."

The hemodynamics of pregnancy have been the target of much investigation in the past. Cardiac output in normal pregnant women has been measured by a number of investigators employing foreign gas techniques.[1-7] Many workers, including Gammeltoft,[3] Stander and Cadden,[4] and Burwell,[6, 7] have demonstrated that cardiac output is increased in pregnancy, reaching a peak early in the last trimester. Particularly noteworthy are the serial studies in the same patient at various stages of pregnancy performed by Gammeltoft[3] and Burwell and his associates.[6, 7] It should be emphasized that, while the methods employing foreign gases generally permit serial study, allowing a comparison of the trend of change in cardiac output at various stages of pregnancy, it has been demonstrated that the absolute values obtained by these methods may be in significant error.[8] Furthermore, these techniques cannot be utilized in the determination of cardiac output during exercise.

Dye-dilution techniques also have been used for the measurement of resting cardiac output in pregnancy.[9] This method has not yet been adequately validated for high output states. The foreign gas and dye-dilution techniques do not, of course, permit the measurement of pressures in the right heart and pulmonary artery.

The modern accepted technique for measurement of cardiac output, fortunately, also permits the simultaneous determination of pressures in the lesser circulation. Pioneer work with this method in pregnancy was carried out by Palmer and Walker[10] and Hamilton[11] in a large series of patients. In these early studies, however, a number of assumptions were made which, as Werko[12, 13] has critically noted, cast serious doubt on the validity of the data. Werko, fully cognizant of the limitations of these earlier studies, utilized scrupulous catheterization technique in his investigation of the cardiac hemodynamics in pregnancy. These studies, however, included observations only early and late in gestation. Furthermore, he made no measurements of the hemodynamic response of the normal pregnant woman to exercise.

The present investigation was undertaken to study the cardiac output and pressure changes in the lesser circulation both at rest and during exercise in normal pregnant women throughout gestation.* Since the catheterization technique does not readily permit serial studies in a single patient, it was necessary to make measurements on groups of patients representing successive stages of gestation.

Material and Methods

Forty-six patients were selected from the Prenatal Clinic of The Mount Sinai Hospital. In none of these was any heart disease demonstrable by clinical, roentgenographic, and electrocardiographic criteria. Each patient was studied once during gestation from the fourteenth week to one day prior to delivery at term.

The patients were grouped as shown in Table I.

With the patients in a basal state without premedication, cardiac catheterization was carried out in classic fashion as follows. A cut down was performed in the left antecubital fossa under local procaine anesthesia. A 125

*Portions of this investigation have been published in detail elsewhere.[14]

cm. cardiac catheter (Fr. 6 through 8) was introduced into the exposed vein and under fluoroscopic guidance was advanced into the thorax and through the superior vena cava, into the right atrium, right ventricle, and pulmonary artery. In half of the cases, the catheter was advanced into a small pulmonary artery until it was wedged. This permitted the measurement of pulmonary "capillary" pressure.[15] Pressures were measured in each of these chambers, and the catheter tip left in the pulmonary artery. Percutaneous puncture of the right brachial artery was performed under local procaine anesthesia and an indwelling needle inserted. Cardiac output was measured by the determination of oxygen consumption (closed circuit in 14 and open system in 32 patients) with simultaneous sampling of blood from the brachial artery and pulmonary artery. In those instances where the open system was employed, the data on the duplicate studies at rest meet the criteria for the steady state.[16]

After two determinations of the cardiac output at rest, the patient, in a recumbent position, exercised by pedaling a stationary bicycle. Pulmonary and brachial artery pressures were measured at 3, 6, 9, and 12 minutes of exercise. Cardiac output was measured after ten minutes of exercise. At twelve minutes of exercise, the catheter tip was withdrawn into the right ventricle and right atrium successively, where pressures were obtained with the patient still exercising.

Pressures were measured with Statham strain gauge pressure transducers employing a cathode ray oscilloscopic recording apparatus. Blood gases were determined by Van Slyke[17] analysis and gas samples analyzed by micro-Scholander[18] technique.

TABLE I. NUMBER OF PATIENTS STUDIED AT PROGRESSIVE PERIODS OF GESTATION

GROUP	WEEK OF GESTATION	NUMBER OF PATIENTS
I	14 to 24	8
II	25 to 27	8
III	28 to 30	10
IV	31 to 35	9
V	36 to 40	11

Formulas

The *cardiac output*, i.e., the volume of blood ejected from the heart per minute, was calculated by the Fick formula which states that the cardiac output (in liters per minute) is equal to the oxygen consumption per minute divided by the arteriovenous oxygen difference (in milliliters per liter) $\left[\text{C.O.} = \frac{\dot{V}O_2}{\text{A-V}}\right]$.

The *stroke volume* (milliliters of blood ejected per beat) is equal to the cardiac output divided by the heart rate $\left[\text{S.V.} = \frac{\text{C.O.}}{\text{H.R.}}\right]$.

The *total peripheral resistance* (TPR) in units of dynes seconds centimeters^{-5} was calculated from the formula

$$\text{TPR} = \frac{1332\ (\text{mean brachial artery pressure in mm. Hg} - \text{mean right atrial pressure in mm. Hg})}{\text{Cardiac output in ml./sec.}}$$

The *left ventricular work* in kilogram meters was calculated from the formula

$$\text{Work in kilogram meters per minute} = \frac{\text{Cardiac output liters/min.} \times 1.055 \times (\text{Brachial artery mean pressure} - 7)\ (13.6)}{1000}$$

TABLE II. MEAN VALUES OF HEMODYNAMIC DATA AT VARIOUS STAGES OF GESTATION

GROUP	WEEK OF PREGNANCY	BODY SURFACE AREA (M^2)	OXYGEN CONSUMPTION C.C./MIN. (M^2)	ARTERIAL BLOOD CAP. (VOL. %)	CARDIAC OUTPUT (L./MIN.)	CARDIAC INDEX (L./MIN./M^2)	A-V DIFF. (VOL. %)	HEART RATE PER MIN.	STROKE VOLUME (C.C.)	$\frac{\Delta \text{ C.O.}^*}{\Delta \text{ VO}_2}$	TOTAL PERIPHERAL RESISTANCE (DYNES SEC. CM.$^{-5}$)
I											
Resting	14-24	1.58	138	14.4	6.53	4.09	3.4	99	70		986
SD†			±12		±0.21	±0.39	±0.2	± 8	± 9		±183
Exercise			230		7.94	5.15	4.5	109	73	1093	904
SD			±34		±1.09	±0.80	±0.2	±11	± 7	±480	—
II											
Resting	25-27	1.64	143	14.4	6.96	4.26	3.4	93	75		1009
SD			±15		±1.19	±0.74	±0.2	± 5	±15		±220
Exercise			237		8.20	5.13	4.7	108	76	1002	813
SD			±35		±1.48	±1.05	±0.3	± 7	±15	±332	±176
III											
Resting	28-30	1.68	137	14.4	6.59	3.93	3.5	94	70		1078
SD			±21		±1.08	±0.65	±0.2	±10	±11		±277
Exercise			236		7.97	4.73	5.0	108	74	838	996
SD			±24		±1.21	±0.71	±0.2	±10	±11	±173	±335
IV											
Resting	31-35	1.63	142	14.7	5.75	3.60	4.0	88	67		1138
SD			±13		±0.72	±0.55	±0.1	±13	±12		±274
Exercise			250		8.11	5.04	5.1	108	75	1231	800
SD			±47		±1.43	±1.00	±0.2	± 7	± 9	±319	—
V											
Resting	36-40	1.61	150	15.2	5.53	3.44	4.4	96	58		1244
SD			±10		±0.72	±0.44	±0.2	± 7	± 8		±152
Exercise			245		6.90	4.25	5.8	110	64	1095	1095
SD			±32		±0.82	±0.39	±0.2	± 9	±11	±323	±79
Normal values			130			3.10	4.3	72	75	600	1200

*$\frac{\Delta \text{C.O.}}{\Delta \text{VO}_2}$ = Increase in cardiac output in c.c. per 100 c.c. increase in O_2 consumption during exercise.

†SD = Standard deviation.

Since it is desirable to compare changes in the various indices, i.e., cardiac output and oxygen consumption, throughout pregnancy, it would be useful to have serial studies in the same patient. The catheterization technique makes this type of serial study difficult because it is a trying procedure. Therefore, comparison of data in the various groups is best made by expressing the indices in terms of square meter of body surface area to eliminate the factor of variation in the size of the patients. The validity of the Du Bois[19] formula for body weight in pregnancy is discussed elsewhere.[14]

Results

The results are presented in Tables II, III, and IV, and Figs. 1-6. Data on the individual cases, and complete statistical analysis have already been published.[14]

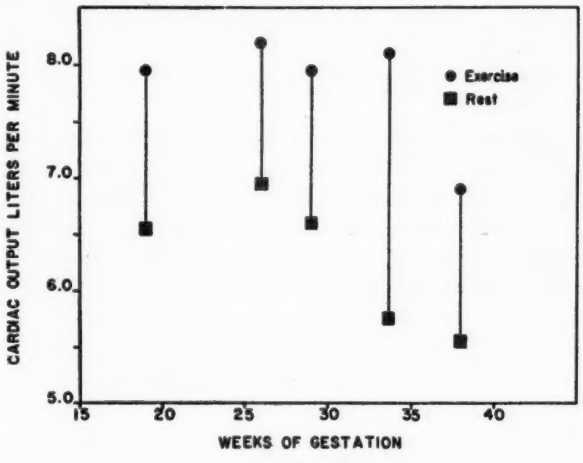


Fig. 1.

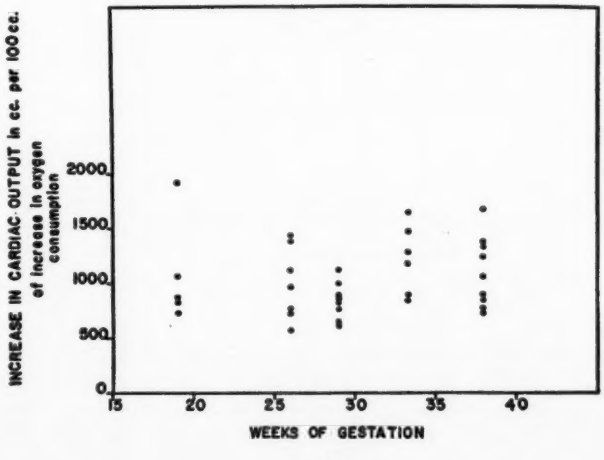


Fig. 2.

Cardiac Output.—The resting cardiac output increased during the twenty-fifth to the twenty-seventh weeks to a maximum 40 per cent greater than values for normal nonpregnant women (Fig. 1). Thereafter the cardiac output fell progressively from its peak in Group II (cardiac index 4.26 ± 0.74 L./min./M^2) until at term the values were only slightly higher than in the nonpregnant

TABLE III. PRESSURES IN RIGH

	UPPER LIMIT NORMAL	GROUP I (8 CASES)				GROUP II (8 CASES)			
		REST		EXERCISE		REST		EXERCISE	
		RANGE IN MM. HG	NUMBER AB-NORMAL	RANGE IN MM. HG	NUMBER AB-NORMAL	RANGE IN MM. HG	NUMBER AB-NORMAL	RANGE IN MM. HG	NUMBE AB-NORMA
Pulmonary artery									
Systolic	30	13-21	0	15-23	0	12-25	0	12-29	0
Diastolic	11	2-9	0	7-9	0	4-8	0	3-16	1
Mean	16	3-6	0	10-14	0	7-16	0	7-19	1
Right ventricle									
Systolic	30	15-21	0	17-23	0	15-27	0	14-26	0
Diastolic	5	0-5	0	0-5	0	2-7	1	1-10	3
Right atrium									
Mean	5	0-3	0	2-5	0	0-2	0	2-7	2
Pulmonary capillary wedge	12	3-6	0			1-11	0		

woman. The average figure for the cardiac index in Group V was 3.44 ± 0.44 L./min./M² compared with the normal figure of 3.10 L./min./M². On exercise, the cardiac output increased normally in all patients as manifested by an increment in cardiac output per 100 c.c. increase in oxygen consumption (Fig. 2). This was greater than the minimal normal response, that is, 600 c.c. per 100 c.c. increase in oxygen consumption per minute.

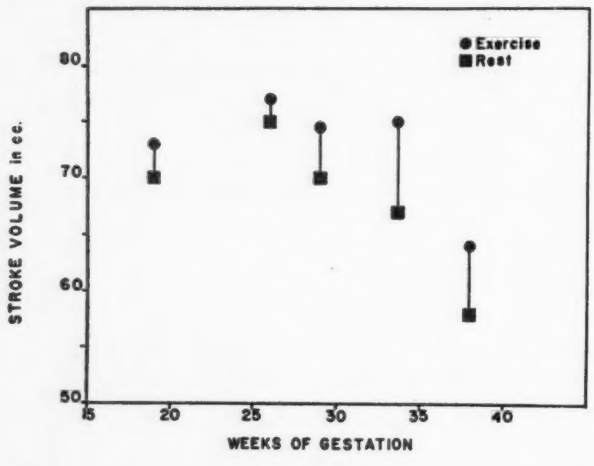


Fig. 3.

Oxygen Consumption and Arteriovenous Oxygen Difference.—As one may see in the formula for cardiac output (previously given), increment in cardiac output could be due to an increase in oxygen consumption or a decrease in the arteriovenous oxygen difference or both. The oxygen consumption increased slightly, reaching a value at term approximately 10 per cent greater than the normal for nonpregnant women. The arteriovenous oxygen difference varied inversely with the cardiac output. The arteriovenous oxygen difference fell to minimum values at the twenty-fifth to the twenty-seventh week (Table II) (3.4 ± 0.2 c.c. per 100 c.c.) and returned gradually to normal values at term (4.4 ± 0.2 c.c. per 100 c.c.).

Stroke Volume.—The high resting level of the heart rate is predominantly responsible for the increased cardiac output, the stroke volume being only

GROUP III (10 CASES)				GROUP IV (9 CASES)				GROUP V (11 CASES)			
REST		EXERCISE		REST		EXERCISE		REST		EXERCISE	
RANGE IN MM. HG	NUMBER AB-NORMAL	RANGE IN MM. HG	NUMBER AB-NORMAL	RANGE IN MM. HG	NUMBER AB-NORMAL	RANGE IN MM. HG	NUMBER AB-NORMAL	RANGE IN MM. HG	NUMBER AB-NORMAL	RANGE IN MM. HG	NUMBER AB-NORMAL
13-22	0	14-28	0	13-22	0	15-23	0	12-20	0	13-30	0
3-11	0	5-16	3	3-9	0	5-11	0	2-11	0	3-15	1
8-15	0	8-20	2	8-15	0	9-15	0	6-15	0	7-20	1
14-26	0	14-27	0	14-23	0	17-24	0	11-22	0	13-27	0
0-7	1	0-7	4	1-10	3	1-10	3	0-4	0	0-6	1
0-4	0	1-7	3	0-6	1	4-8	2	0-4	0	0-5	0
1-8	0			5-8	0			3-9	0		

slightly elevated in the twenty-fifth to the twenty-seventh weeks of gestation (Fig. 3). Of interest is the decrease in stroke volume prior to term, paralleling the decrease in cardiac output, and reciprocal to the change in the anteriovenous oxygen difference.

Total Peripheral Resistance.—There was no significant change in the brachial artery pressures throughout gestation. The peripheral resistance is a function of the pressure drop in the peripheral vascular bed divided by the blood flow. It is apparent, therefore, that without a significant change in

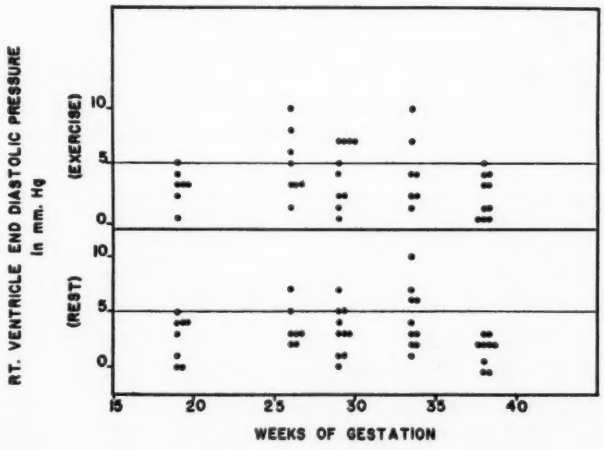


Fig. 4.

the systemic pressure and with a marked increase in flow (i.e., cardiac output), peripheral resistance must be decreased. That this was the case may be seen in Table II. Total peripheral resistance varied reciprocally with cardiac output, being reduced in Groups I, II, and III, and increasing toward normal values at term.

Pressures.—The end diastolic pressure of the right ventricle, which normally does not exceed 5 mm. Hg, was elevated above this value at rest in 5 of 26 patients in Groups II, III, and IV (twenty-fifth to thirty-fifth weeks), being normal in Groups I and V. On exercise, values exceeding 5 mm. Hg were found in 10 patients (Fig. 4).

Pulmonary artery systolic, diastolic, and mean pressures in general were within normal limits (Figs. 5 and 6). On exercise, a definite increase was noted in these values, which, however, still were within normal limits with the exception of a few abnormal figures particularly in the twenty-fifth to thirty-fifth weeks (Table III).

The right ventricular systolic pressure paralleled the pulmonary artery systolic pressure, being normal at rest in all groups and demonstrating an increase on exercise. The exercise values were within normal limits.

Pulmonary "capillary" wedge pressures in all groups were normal in those patients in whom this measurement was made.

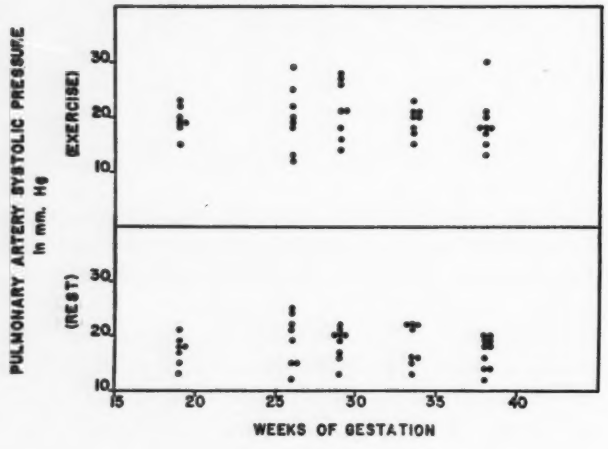


Fig. 5.

Left Ventricular Work.—The work of the left ventricle is a function of the cardiac output, the specific gravity of the blood, and the pressure differential between the left atrium and a systemic artery. Left ventricular work was elevated in Groups I, II, and III, and decreased to normal in Groups IV and V (Table IV).

TABLE IV. LEFT VENTRICULAR WORK (KG. METERS/MIN./M²)

GROUP I		GROUP II		GROUP III		GROUP IV		GROUP V	
PATIENT	REST	PATIENT	REST	PATIENT	REST	PATIENT	REST	PATIENT	REST
A. M.	5 26	G. P.	5.19	A. D.	5.96	D. H.	3.54	C. W.	3.86
M. C.	3.99	V. B.	4.62	G. R.	4.75	E. R.	3.84	M. M.	4.75
J. M.	4.24	R. M.	2.36	M. L.	3.31	A. P.	3.42	D. C.	3.28
E. G.	6.07	N. M.	5.41	C. M.	3.55	L. R.	5.72	M. Mc.	5.14
C. M.	4.72	R. H.	5.06	O. Y.	4.94	M. C.	4.47	A. P.	3.64
A. V.	3.91	M. T.	5.71	E. C.	5.62	Mean	4.20	O. C.	4.49
Mean	4.70	A. V.	4.12	A. L.	3.93			O. B.	4.35
		Mean	4.64	M. P.	4.86			Mean	4.21
				Mean	4.61				

Comment

Cardiac Output.—The observations made do not permit any conclusive statement as to the precise mechanism responsible for the alterations in the hemodynamics. Several possibilities may be invoked to explain the elevation in cardiac output observed. The increase in blood volume in pregnancy, a well-documented observation,[20-23] may explain the hemodynamic changes

which closely resemble those encountered in hypervolemic syndromes associated with congested circulatory states without myocardial damage.[24-27] Since plasma volume remains markedly elevated just prior to term, at which time cardiac output has returned to normal, the hypervolemia cannot be directly correlated with the trend of output changes. A redistribution of blood late in pregnancy with a decrease in the intrathoracic blood volume[13] and pooling of blood in the lower extremities[28] may explain the reduction in cardiac output in the presence of a markedly increased plasma volume.

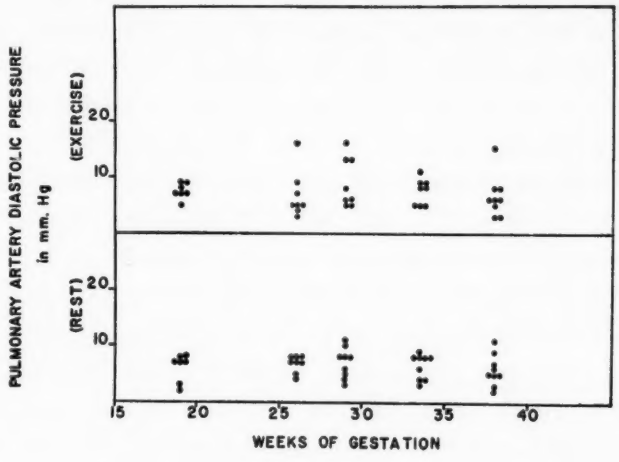


Fig. 6.

The resemblance of the hemodynamics of the pregnant state to those of an arteriovenous fistula have led to the hypothesis that the placenta may behave as an arteriovenous shunt.[29] Considerable anatomical[30, 31] and physiological[32, 33] data not only support this view but also indicate that, as gestation progresses, obliteration of portions of the placental maternal vascular bed takes place[34] with reduction in the arteriovenous shuntlike effect. This, too, may account for the fall in cardiac output prior to term.

In view of the small increment in basal oxygen consumption during gestation, it appears unlikely that the changes in cardiac output are related primarily to the increased metabolic demands of pregnancy. Since no changes in the mean hemoglobin values for each group were noted, anemia likewise could not play a primary role in the changes in cardiac output. It appears that while all these factors may contribute to the changes in cardiac output observed, the alterations are probably chiefly due to the hypervolemia and/or the placental circulation acting as an arteriovenous fistula.

Hemodynamic observations made during exercise furnish information which is not available from the resting studies alone. The stress of exercise often elicits circulatory abnormalities not evident at rest. Normally cardiac output increases to meet the increased metabolic demands of exercise. Failure to do so is a reflection of inadequate myocardial reserve. All of the patients studied except one were able to increase their cardiac output at least 600 c.c. for each 100 c.c. increment in oxygen consumption during exercise. This is

a normal response and indicates adequate myocardial reserve.[35] A smaller increase in cardiac output in response to exercise, in the presence of a normal resting cardiac output, may be regarded as evidence of impaired myocardial reserve.

Pressures.—The elevation of the right ventricular and diastolic pressure during the twenty-fifth to the thirty-fifth weeks in 5 of 26 patients at rest and 10 during exercise was the most significant of the pressure changes noted in the lesser circulation and right side of the heart. Such an elevation, i.e., above 5 mm. Hg, has been regarded as concomitant with failure of the right ventricle. The normal cardiac function as well as the normal response of the cardiac output on exercise in these patients would eliminate the possibility that congestive failure could account for the elevated right ventricular end diastolic pressure in those cases in which it was found. Such elevations of pressure have also been observed in congested circulatory states without heart failure, e.g., in cases of excess salt and water retention as seen in steroid therapy.[25] It is possible, therefore, that the hypervolemia of pregnancy may account for these pressure alterations. The blood volume of pregnant patients is indeed increased, but the augmented blood volume persists until term whereas the right ventricular end diastolic pressure returns to normal. This fall in pressure to normal despite the increased plasma volume could be explained by a redistribution of the increased blood volume into the dependent portions of the body as discussed above.

Another mechanism to account for the increased right ventricular pressure could be an increased intrathoracic pressure due to elevation of the diaphragm. No measurements of the intrathoracic pressure were made in these patients and therefore no statement can be made about the validity of this hypothesis.

Work of the Heart.—The work of the heart[36] is a function not only of the amount of blood put out by the heart pump, but also of the pressure at which the blood is ejected. Since no significant alteration in systemic pressure was noted throughout gestation, it follows that the changes in cardiac work, in general, parallel the alterations in cardiac output. Left ventricular work was higher in the first three groups of patients, falling near term. These physiological data lend credence to the clinical view that even at rest the heart of the pregnant woman has more work to do than in the nonpregnant state. It must be emphasized that this increased burden, documented at rest, is borne constantly, fortunately with some diminution in load as parturition approaches. Despite this burden, however, no impairment in myocardial reserve is demonstrable in pregnant women without heart disease. In pregnant patients with heart disease, on the other hand, such an increased work load may lead to decompensation. In such instances, the cardiac work load must be reduced to the minimum by limiting exertion.

Summary and Conclusions

1. Data on cardiac hemodynamics as studied by cardiac catheterization in 46 normal pregnant women are presented. Observations were made both at rest and during the stress of exercise.

2. There was an increase in cardiac output at rest observed in the earliest period of gestation studied (fourteenth to twenty-fourth weeks) reaching a maximum of 40 per cent greater than that in nonpregnant control women at the twenty-fifth to the twenty-seventh weeks of pregnancy, then falling progressively to normal just prior to term. This was accomplished by a reciprocal change in arteriovenous oxygen difference, while oxygen consumption was only slightly increased.

3. The cardiac output response to exercise was normal in terms of increase in output per unit increase in oxygen consumption in all groups. This indicates that there was no impairment in myocardial reserve.

4. The only remarkable change in pressures in the right heart or pulmonary artery was in the right ventricular end diastolic pressure which was elevated in 5 of 26 patients at rest and in 10 patients on exercise during the twenty-fifth to the thirty-fifth weeks of gestation.

5. Total peripheral resistance was reduced from the fourteenth to the thirtieth week of pregnancy, returning to normal prior to term.

6. Left ventricular work was elevated between the fourteenth and the thirtieth weeks of gestation, and fell prior to parturition.

7. While the exact mechanism responsible for the alterations observed cannot be defined from the data presented, several possibilities to explain the increased cardiac output are discussed. These include the effects of hypervolemia; a possible role of the placental circulation as, in effect, an arteriovenous shunt; and the effect of the increased metabolic demands of pregnancy.

8. These data on normal pregnant women may be used as criteria for the physiological evaluation of the pregnant patient with heart disease. It is hoped that this information will provide a more quantitative approach to the problem of selection of such patients for surgery on the mitral valve, therapeutic abortion, and postdelivery sterilization.

We gratefully acknowledge the encouragement and advice of Drs. Alan F. Guttmacher and Alexander B. Gutman in the preparation of this work. We are also indebted to Dr. Simon Dack for his cooperation and to the Misses Elisa Lopez and Ilse Weinberg and Mrs. Jane Battenelli for technical assistance.

References

1. Lindhard, J.: Arch. f. d. ges. Physiol. **161**: 233, 1915.
2. Weiss, R.: Klin. Wchnschr. **3**: 106, 1924.
3. Gammeltoft, S. A.: Compt. rend. Soc. de biol. **94**: 1099, 1926.
4. Stander, H. J., and Cadden, J. F.: Am. J. Obst. & Gynec. **24**: 13, 1932.
5. Schmidt, R. H.: Monatschr. Geburtsh. u. Gynäk. **90**: 83, 1932.
6. Burwell, C. S., and Strayhorn, W. D., Jr.: J. Clin. Invest. **12**: 977, 1933.
7. Burwell, C. S., Strayhorn, W. D., Flickinger, D., Corlette, M. B., Bowerman, E. P., and Kennedy, J. A.: Arch. Int. Med. **62**: 979, 1938.
8. Hamilton, W. F.: Federation Proc. **4**: 183, 1944.

9. Adams, J. Q.: Am. J. Obst. & Gynec. 67: 714, 1954.
10. Palmer, A. J., and Walker, A. H. C.: J. Obst. & Gynaec. Brit. Emp. 56: 537, 1949.
11. Hamilton, H. F. H.: J. Obst. & Gynaec. Brit. Emp. 56: 548, 1949.
12. Werko, L., Bucht, H., Lagerlof, H., and Holmgren, A.: Nord. med. 40: 1868, 1948.
13. Werko, L.: Acta obst. et gynec. scandinav. 33: 162, 1954.
14. Bader, R. A., Bader, M. E., Rose, D. J., and Braunwald, E.: J. Clin. Invest. 34: 1524, 1955.
15. Hellems, H. K., Haynes, F. W., and Dexter, L.: J. Applied Physiol. 2: 24, 1949.
16. Fishman, A. P., McClement, J., Himmelstein, A., and Cournand, A.: J. Clin. Invest. 31: 770, 1952.
17. Van Slyke, D. D., and Neill, J. M.: J. Biol. Chem. 61: 523, 1924.
18. Scholander, P. F.: J. Biol. Chem. 167: 235, 1947.
19. Du Bois, D., and Du Bois, E. F.: Arch. Int. Med. 17: 865, 1916.
20. Thomson, K. J., Hirsheimer, A., Gibson, J. G., II, and Evans, W. A., Jr.: Am. J. Obst. & Gynec. 36: 48, 1938.
21. Roscoe, M. H., and Donaldson, G. M. M.: J. Obst. & Gynaec. Brit. Emp. 53: 527, 1946.
22. McLennan, C. E., and Thovin, L. G.: Am. J. Obst. & Gynec. 55: 189, 1948.
23. White, R.: Tr. Edinburgh Obst. Soc., Edinburgh M. J. 57: 141, 1950.
24. Youmans, W. B., and Huckins, A. R.: Hemodynamics in Failure of the Circulation, Springfield, Ill., 1951, Charles C Thomas, American Lecture Series.
25. Albert, R. E., and Smith, W. W.: Am. J. Med. 12: 111, 1952.
26. Wilson, J. R., Jr., and Harrison, C. R.: J. Clin. Invest. 29: 251, 1950.
27. Eichna, L. W., Farber, S. J., Berger, A. R., Rader, B., Smith, W. W., and Albert, R. E.: Tr. A. Am. Physicians 67: 72, 1954.
28. Burwell, C. S.: Ann. Int. Med. 11: 1305, 1938.
29. Burwell, C. S.: Am. J. M. Sc. 195: 1, 1938.
30. Spanner, R.: Ztschr. Anat. u. Entwickl. 105: 163, 1935.
31. Earn, A. A., and Nicholson, D.: Am. J. Obst. & Gynec. 63: 1, 1952.
32. Barcroft, J.: J. Physiol. 77: 194, 1933.
33. Barcroft, J.: J. Physiol. 83: 215, 1934.
34. Zeek, P., and Assali, N.: Am. J. Obst. & Gynec. 64: 1191, 1952.
35. Ferrer, M. I., Harvey, R. M., Cathcart, R. T., Cournand, A., and Richards, D., Jr.: Circulation 6: 688, 1952.
36. Dexter, L., Whittenberger, J. L., Haynes, F. W., Goodale, W. T., Gorlin, R., and Sawyer, C. G.: J. Applied Physiol. 31: 349, 1951.

Discussion

DR. MORTIMER BADER.—This study offers us, as Dr. Rose has noted, criteria for the evaluation of the pregnant woman with heart disease. These physiological data supply the quantitative information necessary in assessing the need for therapeutic interruption of pregnancy. Furthermore, the recent remarkable advances in cardiac surgery have made it necessary to have such quantitative information on hemodynamic changes throughout pregnancy in order to insure proper selection of patients for mitral commissurotomy. To re-emphasize the point presented, there is no evidence of inadequate myocardial reserve in normal pregnant women. If such inadequacy exists, it can be regarded as related primarily to heart disease and not to the circulatory alterations in pregnancy. Continuing studies of pregnant women with rheumatic heart disease in our laboratory serve to underscore the importance of the normal data.

DR. EUGENE BRAUNWALD.—I would like to say a few words on the physiology of hypervolemia. Dr. Tinsley Harrison and his group carried out a number of experiments in animals about five years ago and observed hemodynamic changes which resembled very closely the ones seen in normal pregnancy toward the end of the second trimester. By infusing large amounts of normal saline into dogs quite rapidly they were able, first, to raise the right heart filling pressure and, second, to produce increases in cardiac output. Investigations have also been carried out in normal human subjects who were infused with large volumes of plasma and salt-free human albumin. These experiments produced changes which are very similar to those seen in pregnancy. Finally, Dr. Eichna's studies of the congestive circulatory state have shown hemodynamics remarkably similar to those observed in pregnancy, i.e., an elevated cardiac output and right heart filling pressures.

DR. CURTIS L. MENDELSON.—I think it should be mentioned that in 1949 Palmer and Walker of the Post Graduate Medical School of London reported catheterizations in 8 nonpregnant controls and 88 normal pregnant women. They noted a considerable increase in the cardiac output with accompanying changes in right auricular pressure, arteriovenous oxygen difference, and basal metabolic rate. The nonpregnant cardiac output was 4.6 L. per minute and the maximum pregnancy output 5.8 L. per minute. Also the same year Hilary Hamilton of the Royal Infirmary in Edinburgh reported on cardiac output in 24 nonpregnant and 68 normal pregnant women. The normal output of 4.5 L. per minute rose, starting at the tenth to the thirteenth week, and reached a maximum of 5.7 at the twenty-sixth to the twenty-ninth week, returning to normal at the thirty-eighth to the fortieth week (an increase of 27 per cent). Neither investigation reported on exercise tests and undoubtedly the refinements in technique you have heard about in Dr. Rose's paper were lacking. We have performed some 24 cardiac catheterization studies including exercise tests in women with rheumatic heart disease at the New York Lying-In Hospital and I may say that our material in compensated cases corresponds with the data presented. One definite shortcoming of all such studies, including ours, involves determinations in different patients rather than successive determinations in the same patient. Unfortunately this criticism cannot readily be met from the practical standpoint since patients will not submit to repeated studies.

The theory of the placenta acting as an arteriovenous fistula leaves something to be desired, attractive as it may be. Changes in blood pressure and heart size have not been substantiated, and unless one postulates senesence of the placenta, return of cardiac output to normal at term cannot be explained. Alterations in sodium and water metabolism incident to hormonal activity must also play a significant role in the genesis of hemodynamic variations of pregnancy.

Translation of these data into practical use for the obstetrician is not as remote as might be assumed from first glance at these complicated physiological determinations. We must be aware that heart disease is today the single greatest cause of maternal mortality at many large clinics throughout the country where the ravages of hemorrhage, infection, and toxemia have been brought under control. Cardiac catheterization can be safely performed in the pregnant woman and the heart's ability to withstand the predictable hemodynamic burden of pregnancy determined. Application of the type of data presented affords the most accurate means of determining prognosis and rendering proper care. We have cared for over 3,000 pregnant women with organic heart disease at the New York Lying-In Hospital. We now approach the problem of rheumatic heart disease with different types of management: (1) supportive measures for the vast majority, (2) mitral valvulotomy for tight mitral stenosis where supportive measures are inadequate, and (3) therapeutic abortion where supportive measures are inadequate and cardiac surgery not feasible. We have performed mitral valvulotomy in 15 pregnant women without maternal or fetal complications and we believe this operation offers promise of solving the most important problem of heart disease in pregnancy—that of severe mitral stenosis. This procedure has also significantly reduced indications for therapeutic abortion and sterilization. Future progress in intracardiac surgery may indeed some day completely remove these indications.

Dr. Gorenberg has maintained that bed rest is the sole answer to the mortality of heart disease in pregnancy. It should be pointed out that the predictable hemodynamic burdens occur even at complete bed rest. I have long been convinced that no one approach is adequate for all patients. The three methods outlined each play a role in our present concept of management and none is a panacea.

DR. GORENBERG.—I would like to ask, Dr. Rose, what does this mean from the standpoint of work for the heart? I am quite certain that you cannot directly relate changes in cardiac output to cardiac work. There are certainly other factors that play

a part. Could you tell us please from your statistics how much, if any, increase in cardiac *work* results from pregnancy? From a clinical standpoint my experience has been that the so-called "burden" of pregnancy is relatively insignificant.

DR. CHARLES STEER.—Dr. A. J. B. Tillman, of Sloane Hospital, feels that although there may be an increased risk of failure at 28 weeks, the most dangerous time for a pregnant patient with cardiac disease is at term and shortly after delivery.

DR. RICHARD BADER.—In reply to Dr. Gorenberg, it may be stated that we have not yet completed our calculations of the work of the heart.* It is probable that the work of the heart in the pregnant woman is increased.

The question of what significance this material has for the average physician has been answered by Dr. M. E. Bader and Dr. Braunwald. It is certain that we need to know the normal before we can study the abnormal. Furthermore, even if this were solely academic, it would be worth investigating.

In reply to Dr. Mendelson's comments, it should be stated that, to be precise, the first cardiac output studies in pregnancy were done not in 1924 but in 1915 by Dr. Lindhard, and we are all aware that the gas methods were used over the ensuing years. The gas methods gave uniformly lower figures than those obtained by the Fick principle and they cannot be relied upon for absolute values although the data obtained certainly indicated the trend of changes. Second, their use in exercise studies is limited because of rapid recirculation of the blood, and, third, the method does not allow measurement of pressures of the right side of the circulation.

As far as the pioneer work of Walker and Palmer is concerned, Dr. Rose mentioned their work, albeit briefly. They deserve credit for original work but at this point it may be appropriate to mention some of the facts which make interpretation of their data difficult. There are serious defects in these studies. First, they had no fluoroscopic control of the catheter and therefore did not know its location at the times they drew so-called mixed venous blood samples. Second, they did not measure the arterial oxygen saturation. Third, they drew venous blood samples and from the capacity of the venous blood assumed an arterial oxygen content. From this assumption they further calculated the arteriovenous difference. Hilary Hamilton's work was patterned after that of Walker and Palmer, and included the same assumptions. These workers deserve great credit for their early use of catheter technique in pregnant women, but, as Werko has indicated, it is difficult to know exactly what their measurements mean. They offered no adequate data on pressures in the right ventricle and pulmonary artery and none related to the effects of exercise.

Careful work was done in this particular field with the catheter technique by Werko. His studies did not show the marked changes that we found, but he studied the patients in the twelfth and thirty-eighth weeks of gestation which may account for the fact that he did not observe much of a rise in cardiac output. The time period he chose preceded and followed the time of rise in output as we observed it.

As far as the question of complications of cardiac catheterizations is concerned, in the 88 catheterizations 5 patients developed transitory cardiac arrhythmias during the passage of the catheter. Persons experienced in cardiac catheterization will find that this does occur, particularly with the tip of the catheter in the right ventricle. In 2 cases we had to stop because of supraventricular tachycardias which reverted to normal on withdrawal of the catheter.

*Data related to the work of the heart were not presented at the meeting, but are included in the text of this paper.

PROPHYLACTIC PENICILLIN ADMINISTRATION IN THE PREVENTION OF PERINATAL DEATHS

WILLIAM C. KEETTEL, M.D., IOWA CITY, IOWA

(From the Department of Obstetrics and Gynecology, State University of Iowa College of Medicine)

TWO previous communications[1, 2] from the Department of Obstetrics and Gynecology, have recorded our experience with the prophylactic administration of penicillin to women during labor and shortly after delivery. In these studies the penicillin was given intra partum to prevent puerperal infections and resulted in a distinct reduction in the incidence of significant puerperal fevers. In addition, such therapy proved to be an excellent ophthalmic prophylactic in the newborn. The number of cases treated was not large enough to prove statistically whether such treatment resulted in a reduced number of perinatal deaths. Thus, it was felt that a study of the administration of prophylactic penicillin to mothers and infants directed primarily toward the reduction of respiratory complications of the newborn should be undertaken. On theoretical grounds, such prophylaxis looked promising since the uterine cavity can be kept sterile during ordinary labor and delivery.

Whether the amniotic fluid normally enters the fetal respiratory tract "in utero" and during delivery is not proved conclusively. The factors responsible for the inauguration of respiratory movements at birth are as yet unknown. Many have reported respiratory movements in fetal life but such questions as: "Are such movements a normal, constant, physiological part of intrauterine life?" and "Is extrauterine respiration simply their resumption after the interruption by birth?" remain unanswered. Windle[3] felt that such respiratory activity occurs only during artificially produced anoxia or with an excess of carbon dioxide; otherwise, only questionable movements are observed. He concluded that amniotic fluid is inhaled only under pathological conditions.

Snyder and Rosenfeld[4] have demonstrated by animal experimentation that respirations begin prior to birth and that amniotic fluid passes in and out of the lungs. When carbon particles were placed in the amniotic sac of rabbits, widespread dissemination occurred throughout the lung fields in one minute. When the fetus was rendered apneic by an anesthetic given to the mother, no carbon particles were found in the lungs. Similarly, the injection of radiopaque material into the human amniotic sac showed rapid dissemination throughout the lungs and gastrointestinal tract of the fetus. The inhalation of amniotic fluid is thus considered by Snyder[5] to be a normal intrauterine fetal function. Since this explanation of fetal respiration seems so

logical, the question arose whether the intrauterine pulmonary exchange of infected amniotic fluid together with the inhalation of material from the birth canal during and immediately after birth might increase perinatal mortality and morbidity. Since it is possible to prevent bacterial invasion of the uterine cavity by prophylactic administration of antibiotic agents during labor, this study was undertaken to determine whether or not pulmonary complications and perinatal mortality could be reduced.

Material

The patients were delivered in the Department of Obstetrics and Gynecology of the State University of Iowa Hospitals between April 6, 1951, and Dec. 13, 1952. As far as was practicable, alternate patients, as determined by the delivery room nurse, received prophylactic penicillin* according to a predetermined schedule. The untreated patients served as the control series. The only patients excluded from the treatment series were those sensitive to penicillin and those admitted with the cervix fully dilated. All patients were delivered under similar technique by medical students, residents, or the senior staff. Postpartum temperatures were taken by mouth every four hours (excluding 2:00 A.M.) during labor and the postpartum stay which averaged from five to seven days.

In the first half of the experimental series each dose of penicillin consisted of 400,000 units, while in the second half the initial injection was 800,000 units and repeated doses were 400,000 units. The first injection was given as soon as the patient was admitted to the delivery room and subsequent injections were given every twelve hours until delivery. On the average the antepartum injection was given four to six hours prior to delivery. Ten per cent of the patients received two or more doses of the antibiotic. In this study no postpartum injections were given.

In the first half of the treated series (the patients receiving 400,000 units) the term newborn infants were not given penicillin; however, the premature infants received 200,000 units procaine penicillin daily for six days. The newborn infants of the mothers receiving 800,000 units of penicillin received 200,000 units of procaine penicillin daily for six days. The babies in the control series were not treated.

Results

The control series A totaled 897 patients and the experimental Group B, 835. There were 908 children (11 twins) in A and 843 (8 twins) in B. There was a larger number of primiparas in the treated series. The distribution according to financial status, age, and the number of complicated labors and pregnancies was nearly the same.

Despite all attempts to select every other patient, the tendency of the nurses to put the more complicated cases in the treated group is evidenced by the inclusion of only 12 prolonged labors in the control series as against 37 in the penicillin group. Third-stage complications, intrapartum fevers, and prolonged second stages were proportional in both series.

The incidence of induced labor was rather high in both groups; this is due to the type of patients admitted to our service as explained in publications by Plass[6] and Keettel.[7] In Group A, 10 per cent of the labors were induced with premature artificial rupture of the membranes, as compared to 15.8 per cent in B. The incidence of premature spontaneous rupture of the membranes was nearly the same in both groups.

*Dicrysticin was supplied by E. R. Squibb & Sons. Each cubic centimeter of Dicrysticin contained the following: procaine penicillin, 300,000 units; penicillin G potassium, 100,000 units; and dihydrostreptomycin, 0.5 Gm.

The method of delivery is indicated in Table I. The difference in the number of forceps rotation and midforceps operations in the treated series is accounted for by the increased number of prolonged labors. Analgesics, anesthetics, and number and type of perineal repairs were comparable.

TABLE I. METHOD OF DELIVERY

	GROUP A* CONTROL SERIES	GROUP B† PENICILLIN SERIES		
	TOTAL	400,000 UNITS	800,000 UNITS	TOTAL
Spontaneous delivery	777	394	305	699
Low forceps	74	52	45	97
Midforceps	6	10	5	15
Spontaneous breech	21	6	3	9
Breech extraction	12	5	4	9
Cesarean section	16	6	5	11
Version and extraction	2	2	1	3
Total	908			843

*11 twins.
†8 twins.

Fevers were designated as "one-day" when the elevation of temperature (100.4° F. or above) did not persist for more than twenty-four hours; temperature elevations occurring during the first twenty-four hours were included. The "two-or-more-day" fevers included temperature elevations occurring on any two or more days during the puerperium excluding the first twenty-four hours. Intrapartum fevers were diagnosed when the temperature was 100.4° F. or higher during labor. The puerperal courses of the women in the two series on the basis of these criteria are shown in Table II.

TABLE II. FEVER DURING PUERPERIUM

	GROUP A CONTROL SERIES		GROUP B PENICILLIN SERIES			
	TOTAL		400,000 UNITS	800,000 UNITS	TOTAL	
Afebrile	773		438	334	772	
One-day fever	84		25	23	48	
Two-or-more-day fever	40	4.5%	8	7	15	1.8%

The incidence of two-or-more-day fevers was materially reduced in the treated series, there being 40 in the control and 15 in the treated (4.5 and 1.8 per cent, respectively). When the material from the two previous studies[1, 2] was combined, there were 1,718 patients in the control group as compared to 1,682 in the treated series. The number of two-or-more-day fevers was 109, or 6.3 per cent, in the controls as compared to 42, or 2.4 per cent, in the treated patients. This shows conclusively that the incidence of significant fevers can be materially reduced.

The only reactions encountered were mild urticaria in several cases. None of the newborn infants showed any allergic manifestations. There developed no maternal abscesses at the site of injection. In 3 of the premature infants treated with penicillin, abscesses occurred which required incision and drainage. No other untoward reactions were encountered, however.

Perinatal Mortality

There were 59 premature infants born to mothers in Group A and 50 in B (Table III). The weight distribution of the premature infants was comparable. There were 10 deaths of premature infants, 16.9 per cent, in the

control series, and seven, or 14.0 per cent, in the treated series. Of the full-term infants, there were 15 perinatal deaths in Group A (1.7 per cent) and 14 (1.7 per cent) in Group B. Including both full-term and premature infants, there were 12 stillbirths and 13 neonatal deaths in the control group (1.3 and 1.4 per cent). In the treated series there were 12 stillbirths and 9 neonatal deaths (1.4 and 1.1 per cent, respectively).

Anoxia, erythroblastosis, macerated infants stillborn from unknown causes, and congenital defects accounted for most of the stillbirths. The distribution was nearly the same in both groups. The only instances where stillbirths might have been prevented by penicillin prophylaxis were in certain cases of anoxia occurring during labor. Of the 22 neonatal deaths, erythroblastosis, congenital defects, atelectasis, and prematurity accounted for the majority of the deaths and the distribution was nearly the same. There were 6 deaths in the control series due to atelectasis or other respiratory complications, while in the treated series there were only 2 such cases. The numbers are not large enough to be statistically significant, however.

TABLE III. PERINATAL MORTALITY

	GROUP A CONTROL SERIES			GROUP B PENICILLIN SERIES		
		DEATHS			DEATHS	
	TOTAL	NUMBER	%	TOTAL	NUMBER	%
Premature	59	10	16.9	50	7	14.0
Full-term	849	15	1.7	793	14	1.7
Total	908	25	2.7	843	21	2.5

Comment

In spite of the evidence here presented that large doses of penicillin administered prophylactically during labor will reduce the incidence of postpartum fevers, it seems questionable whether such prophylaxis should be made a routine practice in the case of the normal woman who can be expected to be delivered without difficulty. There is always danger that reliance on such protection will lead to violation of the ordinary surgical principles essential to good obstetrical practice. Accumulating evidence indicates, however, that, especially in prolonged labors, difficult operative deliveries, or certain antepartum complications, the administration of antibiotics in addition to the usual supportive measures provides additional safety for the mother and perhaps for her baby. The further inference to be drawn from these data is that those conditions which provoke transient febrile responses in the puerperium are not susceptible to control by penicillin, and that use of the antibiotics is not necessary for their control. By contrast, fevers of longer duration appear to be largely on the basis of infections with susceptible organisms, so that therapeutic penicillin early in the course of the complication may be advisable.

It was hoped that the prophylactic administration of penicillin to the patient in labor would act as a bacteriostatic agent and thus would reduce the incidence of intrauterine contamination of amniotic fluid and would materially reduce perinatal mortality. This present study as well as the other two previous reports have not borne out this assumption. The number of full-term stillborn infants and neonatal deaths was the same. There was a slight reduction in the mortality of premature infants in the treated series and there

were also fewer deaths from atelectasis. But the number of cases was too small to draw any definite conclusion. There were no cases of hyaline membrane disease reported either in the control or treated series. It is interesting to note that the one instance of intrauterine pneumonia occurred with the mother receiving prophylactic penicillin. Labor was induced electively in this primiparous patient with artificial rupture of the membranes. There was a latent period of nine hours before effective labor started. Labor was very short and the patient received the prophylactic penicillin only one half hour prior to the delivery; thus the medication was given too late to have any effect.

Conclusions

1. The intramuscular administration of large doses of penicillin to parturient women does materially reduce the incidence of two-or-more-day fevers. There is probably no reason for prophylactic administration of penicillin to normal women, but the drug should be given prophylactically to women with prolonged and difficult labor and to those potentially infected.

2. The intramuscular administration of large doses of penicillin to parturient women and also to the newborn infant has not resulted in a significant reduction in perinatal deaths either in the full-term or premature infant and cannot be recommended as a routine practice.

References

1. Keettel, W. C., Scott, J. W., and Plass, E. D.: Am. J. Obst. & Gynec. **58**: 335, 1949.
2. Keettel, W. C., and Plass, E. D.: J. A. M. A. **142**: 324, 1950.
3. Windle, W. F.: Asphyxia Neonatorum, Springfield, Ill., 1950, Charles C Thomas, Publisher, pp. 44-51.
4. Snyder, F. F., and Rosenfeld, W.: Am. J. Obst. & Gynec. **36**: 363, 1938.
5. Snyder, F. F.: Obstetric Analgesia and Anesthesia, Philadelphia, 1949, W. B. Saunders Company, pp. 29-99.
6. Plass, E. D., and Seibert, C. W.: Am. J. Obst. & Gynec. **32**: 785, 1936.
7. Keettel, W. C., Diddle, A. W., and Plass, E. D.: Am. J. Obst. & Gynec. **40**: 225, 1940.

A REVIEW OF VAGINAL DELIVERY FOLLOWING CESAREAN SECTION, FROM PRIVATE PRACTICE

PAUL E. LAWLER, SR., M.D., MATTHEW J. BULFIN, M.D., FRANK C. LAWLER, M.D., AND PAUL E. LAWLER, JR., M.D., CHICAGO, ILL.

(From the Department of Obstetrics and Gynecology, The Little Company of Mary Hospital)

DURING the past ten years there has been a slow but steady rise in the incidence of cesarean sections throughout the country. This has been apparent from the many reports in the literature from university hospitals and teaching centers, and from private hospitals as well. Colvin[3] states that the average cesarean section rate in large maternity centers has risen to 6.2 per cent. New York Lying-In Hospital reports a 5.1 per cent incidence for the year 1952.[24] Beth Israel Hospital reports a 6.7 per cent rate for a four-year period, 1950 through 1953.[20]

With this increased incidence of cesarean sections, it is quite apparent that the indications are being broadened yearly. The leading indication at a high percentage of hospitals is repeat section. As an example of the rising incidence of repeat sections throughout the country we cite the statistics reported from Flushing Hospital in New York on the percentage of repeat sections during the past twenty years.[21]

1937-1941	18 per cent
1941-1946	31.5 per cent
1947-1951	40.6 per cent

"Once a section, always a section" is still the main dictum at a majority of teaching centers. There are relatively few major hospitals in the country where a substantial percentage of patients with previous cesarean sections are allowed to be delivered vaginally. A list of hospitals and their statistics on vaginal delivery following cesarean section are presented in Table I.

We wish to mention one of the more cogent reasons for this particular study. Our patients come from a residential neighborhood on the south side of Chicago that is dominantly Roman Catholic. No tubal ligations are done by our group; no contraceptive devices are recommended or given. Those who desire such aids would go elsewhere for medical services. We are aware that repeat cesarean sections, with their greater financial burden, slower recovery, and their aspect of a major surgical operation, might well act as a deterrent to many young couples desirous of more children. The moral and religious aspect involved has been quite apparent in our practice. Although we believe that any woman who has had a previous cesarean section should

be prepared to undergo another if necessary, we feel more strongly that she should be allowed to demonstrate her capacity to be delivered vaginally provided the necessary conditions are fulfilled.

TABLE I. VAGINAL DELIVERY FOLLOWING CESAREAN SECTION

INSTITUTION AND AUTHOR	YEAR	TOTAL CASES	VAGINAL DELIVERY
Margaret Hague Cosgrove[5]	1950	500	35.8%
Lewis Memorial Schmitz and Gajewski[22]	1951	448	32.6%
New York Lying-In[28]	1951	445	38.7%
Boston Lying-in Lane and Reid[14]	1953	114	16.0%
Leeds Maternity Hospital Lawrence[15]	1952	195	21.6%
Cornell University Wilson[28]	1952	167	33.6%

The senior authors of this paper have been delivering previously sectioned patients vaginally since 1932 and 1941, respectively. It was felt that the statistics accumulated from their private practice during the years 1932 through 1955 would be of value in arriving at a decision as to the wisdom of this policy.

The following statistics represent cases that occurred in the senior authors' (P. E. L. and F. C. L.) private practice or cases for which they served as consultants. All of these patients were delivered at The Little Company of Mary Hospital* (Table II).

TABLE II. METHOD OF DELIVERY IN PATIENTS WITH PREVIOUS CESAREAN SECTION

Total number of patients	165		
Delivered by repeat section		109	66%
Delivered vaginally		56	34%
Sectioned again after failure of trial labor	3		5%
Total patients with previous section who were delivered vaginally after having been seen in consultation—delivered by other doctors	14		
Total patients delivered vaginally	70		

Of the 3 patients who failed to be delivered vaginally after a trial of labor, 2 were sectioned after eight hours of fairly strong pains when satisfactory dilatation failed to occur. The third patient was examined after seven hours of ineffectual pains and the head was still not engaged. She was also operated upon. In all 3 of these cases, both mother and baby had an uneventful postpartum course.

TABLE III. ORIGINAL INDICATION FOR CESAREAN SECTION IN PATIENTS DELIVERED VAGINALLY

REASON FOR PREVIOUS SECTION	NUMBER OF PATIENTS
Toxemia	15
Placenta previa	14
Abruptio placentae	13
Cephalopelvic disproportion	17
Unknown	11

*The cesarean section rate at The Little Company of Mary Hospital during the years 1952, 1953, and 1954 was 1.8 per cent, representing 256 cesarean sections in 13,613 deliveries.

In some of the cases in which pregnancy was terminated for cephalopelvic disproportion, in reality the operation was done because of inefficient functioning of the uterine muscle resulting in a prolonged, desultory type of labor (Table III). The indication for previous section in 11 of our cases could not be satisfactorily determined. In all of these cases the original section had been performed elsewhere, and accurate data could not be obtained.

Table IV shows that 42 patients had one delivery and 24 had 2 to 5 vaginal deliveries after cesarean section.

TABLE IV. NUMBER OF VAGINAL DELIVERIES PER PATIENT FOLLOWING CESAREAN SECTION

NUMBER OF VAGINAL DELIVERIES	NUMBER OF PATIENTS
1	42
2	11
3	10
4	1
5	2

In our series of 104 vaginal deliveries, no uterine ruptures occurred. There were 3 infant deaths, a 2.9 per cent mortality rate. Prolapse of the cord accounted for 2 of these deaths. The third infant died six hours after birth of hydrocephalus.

Table V shows that 24 per cent of the patients had spontaneous and the others had operative deliveries.

TABLE V. METHOD OF DELIVERY EMPLOYED IN THE 104 VAGINAL DELIVERIES

Spontaneous	24
Low forceps	71
Scanzoni rotation, midforceps	4
Breech extraction	3
Version and extraction	2

One of the two versions was done on a second twin. Another version was done in the following case:

A 35-year-old para ii, gravida iii, with a history of previous cesarean section for placenta previa, entered the hospital ten days before term in active labor. Examination on admission revealed 7 cm. dilatation with a transverse presentation, a hand presenting and prolapsed cord. No fetal heart tones were heard. The patient was delivered by version and extraction of a 7 pound stillborn male infant. The uterine scar was explored and found to be well healed. The patient made an uneventful recovery.

One patient in our series after an initial cesarean section for transverse presentation with her first pregnancy in 1949, delivered a set of twins in 1950, a single female 6 pound infant in 1952, and a second set of twins in 1954.

The 4 (2.5 per cent) uterine ruptures all occurred in patients who were scheduled for repeat section, and all 4 were discovered only when the abdomen was opened at the time of elective section. Each rupture was of the incomplete "window rupture" type. At laparotomy, the membranes were visible in the old scar. Two of these cases required cesarean hysterectomy because of the size of the rent and the poor condition of the tissues. Both the other ruptures were successfully repaired with three layers of closure. One of these 2 patients subsequently became pregnant and was delivered by repeat elective section.

Three out of 4 of the incomplete uterine ruptures in our series occurred in women who had had two previous sections. In each of these 3 cases, the first section had been of the classical type, while the subsequent section was low cervical.

The patient in our series who had six cesarean sections had a well-healed scar; the 2 patients who had five cesarean sections likewise had strong, well-supported uterine scars. We believe that these patients can still be successfully delivered abdominally in future pregnancies (Table VI).

TABLE VI. NUMBER OF REPEAT SECTIONS

NUMBER OF SECTIONS	NUMBER OF PATIENTS
2	74
3	28
4	4
5	2
6	1

We agree with Cosgrove[4] that the practice of sterilizing a woman after two or three cesarean sections is medically archaic. We fail to understand the seeming omniscience of certain individuals who decree that a woman's fecundity shall be automatically terminated after two or three cesarean sections (Table VII).

TABLE VII. WANING FECUNDITY OF PATIENTS DELIVERED BY CESAREAN SECTION EXCLUSIVELY

	NUMBER OF CESAREAN SECTIONS					
	2	3	4	5	6	7
Matthews[17] (1939)	279	48	3			
Barrett[1] (1939)	163	26	2			
Free[10] (1945)	167	26	1			
McSweeney and Hassett[16] (1948)	349	181	52	16	7	1
Schmitz and Gajewski (1951)	87	31	8	2		
Margaret Hague[4] (1950)	269	53	10			
Lawler and Bulfin (present study)	74	29	4	2	1	

Although maternal fatalities following cesarean section are at an all-time low, it does not follow that the procedure is without hazard. Newberger[18] points out that 43.2 per cent of all maternal deaths in Illinois in 1948, 1949, and 1950 followed cesarean section, and the incidence of cesarean section in the state at that time was 3.7 per cent.

Fetal mortality is three times as great in cesarean section as in vaginal deliveries.[6] Thirty-five per cent of the premature infants in a series of cesarean sections from a small urban hospital resulted from miscalculation of the term of gestation.[23]

At the Denver General Hospital a 50 per cent total fetal loss occurred in elective repeat sections.[13] Four of the infants weighed less than 2,500 grams; hence poor timing of section and inaccurate estimate of fetal size are constantly threatening the obstetrician who does repeat sections. This also refutes the growing contention that cesarean section guarantees a living, healthy infant.

It is not true that the higher the section rate, the lower the fetal mortality. There is a point of diminishing returns which D'Esopo[7] has established at 7 per cent.

Yet there has been a plea for further widening of indications for cesarean section so that upward of a 10 per cent incidence will prevail. "Ideally we should have only two types of deliveries, normal vaginal deliveries, including

elective low forceps, and cesarean sections. The authors[12] from whom this is quoted are of the opinion that every difficult vaginal delivery should be regarded as an error in judgment by the attending obstetrician.

Cesarean section has two hazards, the immediate hazard of operation and the late hazard of uterine rupture in subsequent pregnancies. This late hazard cannot be forestalled altogether by repeat section because some scars rupture several weeks before section is scheduled.

It is likewise obvious that women who are delivered vaginally have an over-all lower morbidity rate than women who are reoperated upon. In a review of 1,000 cesarean sections Sullivan and Campbell[26] report a 14.6 per cent morbidity rate.

With the incidence of cesarean section increasing yearly, the problem of delivery after previous section is likewise going to be met more frequently. Eames[8] stated that this problem arises now in 1.5 of 100 pregnancies. The greatest deterrent to allowing vaginal delivery after previous cesarean section is the universal fear of rupture of the previous uterine scar. Table VIII shows some of the statistics on the likelihood of rupture of the cesarean section scar during pregnancy.

Twenty-four per cent of uterine ruptures occurred before the thirty-seventh week in previously sectioned patients.[8] Thus one-fourth of the patients experienced rupture before the advocates of repeat section would have undertaken any active treatment. According to Eames' statistics, the incidence of rupture of the uterus occurring in trial vaginal delivery is 1 per cent with low cervical scars and 2 per cent with classical scars.

No author differentiated between actual uterine rupture and herniation of intact membranes through the old scar with no evidence of rupture of the uterine peritoneum.

TABLE VIII. RUPTURE OF CESAREAN SECTION SCAR DURING PREGNANCY

AUTHORS AND CLINIC	NO. OF PREGNANCIES	RUPTURE OF CESAREAN SCAR	INCIDENCE %
Lane and Reid,[14] 1939-1952 Boston Lying-in	583 sections 89 vaginal deliveries	16 1	2.7 1.1
Schmitz and Gajewski,[22] 1931-1945 Lewis Memorial	106 sections 51 vaginal deliveries	3 0	2.7 0
Tollefson,[27] Los Angeles	227 sections	3	1.2
Studdiford and Decker[25] Bellevue Hospital, New York	176 sections	7	4.0
Wilson,[28] 1932-1950 Cornell University	578 sections 365 vaginal deliveries	15	1.6
Chesterman[2] University of Sydney	1,874 cases	33	1.76
Lawler and Bulfin Little Company of Mary	157 repeat sections 104 vaginal deliveries	4 ("window") 0	2.5 0

Let us remember that the type of rupture that is reported with low cervical scars is usually found at the time of repeat section. The previous incision has separated so that a portion of the chorionic sac and its contents is uncovered and clearly visible after the bladder flap has been displaced downward. The area is usually 2 to 5 cm. in length. Many of these cases can undoubtedly be repaired after delivery. There have been a few cases reported recently where subsequent pregnancies have occurred and normal infants have been delivered at term by another section.[9]

Greenhill[11] in his 1953 *Year Book* states that "an anatomically weak scar does not necessarily presuppose inability to withstand the distention caused by pregnancy or the strain of labor, at least in the lower segment."

The maternal mortality associated with rupture of a low cervical scar during pregnancy or labor is exceedingly small. In a review of 22 uterine ruptures during 35,253 pregnancies, Parker and Jones[19] showed that 4 out of 7 mothers died who had spontaneous ruptures; 4 out of 8 mothers who had traumatic ruptures died; no mothers in 7 cases of postcesarean ruptures were lost. There was no clinical shock in any of the postcesarean ruptures. In Sullivan and Campbell's[26] review of 1,000 cesarean sections in the era of modern obstetrics all three ruptures of the uterus occurred in patients with a previous classical section.

Eames states that the maternal mortality with rupture of a low cervical scar in trial vaginal delivery is 0.01 per cent (teaching institution statistics). He attributes this fact to the comparative avascularity of the old scar so that when the abdomen is opened it is not at all unusual to discover only minute amounts of blood present. Hence, he states, the possibility of rupture of this type of scar during labor is by no means to be disdained, but neither is it to be viewed with abject terror.

We believe that successful vaginal deliveries following previous cesarean sections depend on a number of factors. Our policy with regard to selection and management of patients for vaginal delivery consists of the following:

1. The original section must not have been done for a definitely contracted pelvis.

2. If the section were done elsewhere, efforts are made to secure all pertinent data from the previous doctor.

3. The type of section done previously is most important. We do not attempt to deliver any patients vaginally who had a classical section previously. Almost all of our vaginal deliveries were performed in patients who previously had a low cervical type of section.

4. The type of postoperative course that the patient had with her cesarean section is evaluated. There must have been no postoperative fever, wound infection, or dehiscence.

5. The patient must be psychologically receptive to the idea of vaginal delivery. We spend a great deal of time explaining the advantages of vaginal delivery over cesarean section to the patient. We also advise her, however, that another cesarean section might be decided upon even after she has been in labor several hours. We do not minimize this possibility.

6. The patient is instructed very carefully so that the presence of any unusual abdominal pain during the latter stage of pregnancy is to be reported immediately to the doctor.

7. No induction of labor is permitted.

8. The patient is carefully examined at the beginning of labor to determine the position and size of the fetus, the presence of engagement, and the status of the cervix and membranes. If there is any question as to fetal position, a pelvic x-ray is taken and evaluated.

9. Typing and cross-matching are done on all patients who are to have a trial of labor, and blood is immediately available.

10. The attending doctor must assume the complete management of the patient once labor has begun and not leave the labor rooms. The patient must be watched continually.

11. A thorough manual examination of the uterus is made immediately after delivery of the placenta in order to evaluate the uterine scar. Relatively very few thin weakened scars were found in our series of patients who were delivered vaginally.

Undoubtedly, a doctor's attitude toward such a controversial question as this is based necessarily on his own experience. From our results in this over-all statistical survey, we are more convinced than before that vaginal delivery following previous cesarean section can be a safe and most rewarding experience for the mother. Once we have successfully delivered a woman vaginally after cesarean section, we feel that her outlook for future pregnancies is much improved. She certainly is not as much the "obstetrical cripple" as the woman who has repeat cesarean sections. Cosgrove cites the case of one woman who was delivered of eleven babies vaginally after an initial cesarean section for eclampsia.

Summary

1. One hundred four cases of vaginal delivery following cesarean section have been reviewed from private practice. There were no ruptures of the uterine scar. There was no maternal mortality. The uncorrected fetal mortality was 2.9 per cent.

2. One hundred fifty-seven cases of repeat cesarean section have been reviewed from private practice. There were four incomplete "window ruptures" of the uterus among these cases, and these were discovered only at the time of elective repeat cesarean section. Two of these incomplete ruptures were repaired, and two required cesarean hysterectomies. There was no maternal or infant mortality in any of these ruptures.

Conclusions

1. All the factors that render cesarean section a relatively safe procedure—blood, antibiotics, chemotherapy, and well-trained obstetrical assistants—also operate nowadays to make vaginal delivery after cesarean section equally safe, and more rewarding to the patient.

2. Miscalculation of fetal size and stage of gestation is constantly threatening the obstetrician who does repeat sections.

3. Rupture of a low cervical scar during pregnancy or labor does not occur as frequently as does rupture of a classical scar. Most of these ruptures are of the incomplete type, and in many instances can be successfully repaired. The maternal mortality rate with such a rupture is extremely low, and more infants survive than would with rupture through a classical scar.

4. The number of patients with previous cesarean sections is increasing yearly. We believe that many women with a history of a low cervical cesarean section can be safely delivered vaginally under certain definite conditions.

5. We fail to understand how two or three repeat cesarean sections per se warrant a sterilization operation. We do not believe that cesarean hysterectomies as sterilizing procedures are necessary or desirable.

References

1. Barrett, A. L.: AM. J. OBST. & GYNEC. **37**: 434, 1939.
2. Chesterman, J. N.: J. Obst. & Gynaec. Brit. Emp. **60**: 684, 1953.
3. Colvin, E. D.: AM. J. OBST. & GYNEC. **64**: 473, 1952.
4. Cosgrove, R. A.: Trans. Fifth Am. Cong. on Obst. & Gynec. (supp. vol. AM. J. OBST. & GYNEC.) **64**: 545, 1952.
5. Cosgrove, R. A.: J. A. M. A. **145**: 884, 1951.
6. Davis, M. E.: S. Clin. North America **33**: 101, 1953.
7. D'Esopo, D. A.: AM. J. OBST. & GYNEC. **58**: 1120, 1949.
8. Eames, D. H.: AM. J. OBST. & GYNEC. **65**: 944, 1953.
9. Editor's Note: Obst. & Gynec. Surv. **7**: 194, 1952.
10. Free, E. G.: AM. J. OBST. & GYNEC. **49**: 401, 1945.
11. Greenhill, J. P.: The 1953 Year Book of Obstetrics and Gynecology, Chicago, 1953, The Year Book Publishers, Inc., p. 201.
12. Harris, J. M., et al.: West. J. Surg. **59**: 337, 1951.
13. Ingraham, C. B., Bruns, P. D., and Hansen, H. A.: Obst. & Gynec. **2**: 230, 1953.
14. Lane, F. R., and Reid, D. E.: Obst. & Gynec. **2**: 54, 1953.
15. Lawrence, R. F.: J. Obst. & Gynaec. Brit. Emp. **60**: 237, 1953.
16. McSweeney, D. J., and Hassett, A. J.: New England J. Med. **239**: 254, 1948.
17. Matthews, H. B., and Achen, H. S., Jr.: AM. J. OBST. & GYNEC. **38**: 956, 1939.
18. Newberger, C.: J. A. M. A. **149**: 328, 1951.
19. Parker, J. C., and Jones, G. R.: AM. J. OBST. & GYNEC. **62**: 330, 1951.
20. Rubin, H. W., Burke, L., and Rosenfeld, H. H.: New England J. Med. **249**: 719, 1953.
21. Schaefer, G., and Carpenter, F.: AM. J. OBST. & GYNEC. **65**: 935, 1953.
22. Schmitz, H. E., and Gajewski, C. J.: AM. J. OBST. & GYNEC. **61**: 1232, 1951.
23. Schneider, B.: AM. J. OBST. & GYNEC. **68**: 1065, 1954.
24. Smith, E. F., and MacDonald, F. A.: Obst. & Gynec. **2**: 593, 1953.
25. Studdiford, W. E., and Decker, W. H.: Fetal and Neonatal Risks Related to Cesarean Section, Bull. New York Acad. Med. **28**: 640, 1952.
26. Sullivan, C. L., and Campbell, E. M.: Obst. & Gynec. **5**: 669, 1955.
27. Tollefson, D. G.: South. M. J. **46**: 290, 1953.
28. Wilson, A. L.: AM. J. OBST. & GYNEC. **62**: 1225, 1951.

1150 WEST 78TH STREET

DILATATION OF THE UTERINE CERVIX OF THE SOW FOLLOWING TREATMENT WITH RELAXIN*

M. X. Zarrow, Ph.D., G. M. Neher, Ph.D., D. Sikes, D.V.M., D. M. Brennan, M.S., and J. F. Bullard, D.V.M., Lafayette, Ind.

(From the Department of Biological Sciences and the Department of Veterinary Science, Purdue University)

ALTHOUGH relaxin was first described by Hisaw[1] in 1926, it is still one of the least known hormones. The original work by this investigator and his collaborators[2, 3, 4] on the presence and identity of this substance has been confirmed by others[5, 6] and extended to indicate the presence of this hormone in increasing amounts during pregnancy.[7-11] Recently, many new physiologic effects have been ascribed to relaxin so that the hormone is now beginning to assume a new importance. Actually, Hisaw and Zarrow[12] in 1951 and Frieden and Hisaw[6] in 1953 concluded from the available evidence that relaxin is a true hormone of pregnancy and that it produces a number of different effects. It now appears that the specific effect produced by relaxin may, in part, be dependent on the species.

The present report is concerned with the phenomenon of dilatation of the uterine cervix following treatment with relaxin. This phenomenon has been reported in the cow[14, 15] and briefly indicated as occurring in the sow.[15] Since the ovary of the pregnant sow is the richest source of relaxin[9] and since no physiologic action of this hormone in the sow was previously known, an intensive study was undertaken of the role of relaxin in the sow. The present report discusses in detail the effect of relaxin and stilbestrol on the uterine cervix of the young, castrated sow.

Materials and Methods

Sows were castrated at an approximate age of 8 months and used several months later in these experiments. Dilatation of the cervix was measured by the passage of aluminum rods with diameters graduated in 1/8 inches up to a maximum of 2 inches. These rods were machine tooled and greased prior to insertion in the vagina and cervix. The rods were inserted with a gentle rotating pressure until the entire cervix had been traversed. In all instances the cervix was first tested with the rod of the smallest diameter and this was repeated with rods of increasing diameter until a size was attained which could not be passed. Prior measurements on a sow of comparable age at postmortem indicated the length of the rod that had to be passed in order to traverse the cervix.

All the steroid hormones were dissolved in oil and injected intramuscularly. Relaxin† was dissolved in an aqueous medium and injected three times daily[16] via the intramuscular route.

*Aided in part by a grant from the Ortho Research Foundation.

†The relaxin used in these experiments was supplied under the trade name of Releasin through the courtesy of Dr. Robert L. Kroc, The Warner-Chilcott Laboratories.

Histochemical studies for glycoproteins present in the reproductive tract were carried out using the Hotchkiss-McManus technique as modified by Perl and Catchpole.[16] The tissue was removed and immediately frozen at minus 150° C. with isopentane and liquid nitrogen. The frozen tissue was then dehydrated at minus 35° C. and stained by the Schiff reagent. Total water analyses were carried out in several instances by drying the tissue to a constant weight at 105° C.

Results

The diameter of the uterine cervix of the sow was found to vary from 2/8 of an inch to 1 1/8 inches. It is apparent from the data in Table I that the diameter of the cervix of the multiparous sow was much larger than that observed in the gilt. The diameter of the cervix of the gilts varied from 1/4 to 3/8 inch and in the multiparous animal from 7/8 to 1 1/8 inches. Within the time limits of this experiment no marked changes were observed in the diameter of the uterine cervix following castration in the gilt. It appears that cervical dilatation occurs with the first pregnancy whereas in the nonpregnant beast dilatation does not occur. Measurements were carried out for slightly less than a year in nontreated castrated sows and no marked changes were observed in the diameter of the cervix during this period.

TABLE I. DIAMETER OF UTERINE CERVIX OF THE SOW

ANIMAL NO.	BODY WEIGHT (POUNDS)	CONDITION	DIAMETER OF CERVIX (INCHES)	
			INDIVIDUAL	AVERAGE
1	390	Multiparous	1 1/8	
2	350	Multiparous	7/8	1
3	262	Gilt	3/8	
4	250	Gilt	3/8	
5	232	Gilt	3/8	
6	260	Gilt	1/4	
7	327	Gilt	3/8	
8	279	Gilt	1/4	
9	271	Gilt	3/8	3/8

TABLE II. DILATATION OF THE UTERINE CERVIX OF THE GILT* FOLLOWING TREATMENT WITH STILBESTROL AND RELAXIN

SOW NO.	HORMONE TREATMENT				RELAXIN DAILY FOR 4 DAYS (G. P. U.)	DIAMETER OF UTERINE CERVIX† (INCHES)
	STILBESTROL		PROGESTERONE			
	MG. DAILY	NO. OF DAYS	MG. DAILY	NO. OF DAYS		
Control						1/2 to 3/8
R. B.						1/4
Bl. Back	5	11				1/4 to 3/8
	5	11	1			3/8 to 1/2
286			100	11		3/8 to 1/2
					15,000	
177	5	7	200	4		3/8 to 1/2
146	5	7	100	4		3/8 to 1/2
288	5	7			15,000	1/2 to 7/8
262	5	7			15,000	1/4 to 1
W. Back	5	7			36,000	3/8 to 1
Bl. Hip	5	7			27,000	3/8 to 1
No tag	5	7	100	4	15,000	1/2 to 1 1/4
Gilt						2/8 to 3/8
Mature Sow						3/4 to 7/8

*A gilt is a sexually mature sow that has not farrowed.
†These columns represent the minimum and maximum values obtained.

It is apparent from the data in Table II that cervical dilatation may occur as a result of the combined action of stilbestrol and relaxin. Stilbestrol alone at 5 mg. per day for 7 to 11 days had no significant effect on the diameter of the cervix. Similarly, progesterone (100 to 200 mg. per day) when given alone or in combination with stilbestrol failed to influence the diameter of the uterine cervix. Treatment of 5 gilts with 5 mg. of stilbestrol daily for 7 days, followed by three daily injections of relaxin for 4 days, induced a marked and highly significant dilatation of the uterine cervix as evidenced by the passage of aluminum rods with a diameter of 1 inch (Table II). Under the conditions of this experiment, a maximum effect was obtained with a dosage of 15,000 G. P. U. (guinea pig units) of relaxin per day. Greater dosages of 27,000 and 36,000 G. P. U. per day failed to produce any greater increase in the dilatation of the uterine cervix. The highest dosage, however, resulted in hastening the time for the maximum response to occur (Fig. 1).

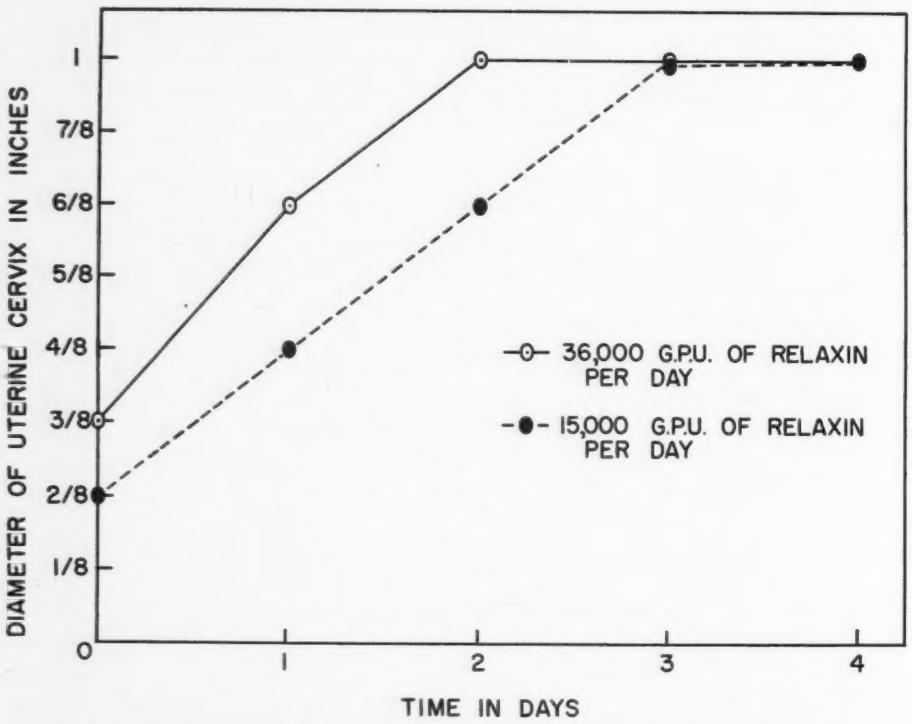


Fig. 1.—Dilatation of the uterine cervix of the castrated sow pretreated for 7 days with stilbestrol followed by treatment with relaxin for 4 days. A measurable response is seen within 24 hours.

In an attempt to determine whether the mechanism of action of relaxin was comparable to that described for the pubic symphysis of the guinea pig, both the water content and the degree of depolymerization were determined. It may be noted from the data in Table III that stilbestrol caused a marked increase in the water content of the vulva, cervix, and uterus as compared with those of the castrated controls. Treatment with a combination of both stilbestrol and relaxin caused a further increase of approximately 1 per cent in the cervix and uterus of these animals as compared with stilbestrol-treated animals and a marked increase of 3 per cent in the vulva. These changes appear to be significant but no definite statement can be made since only one

animal was used in each group. The results of the McManus-Hotchkiss reaction indicated a very slight degree of depolymerization after stilbestrol and a marked degree of depolymerization after treatment with stilbestrol and relaxin. These changes were present in the vulva, cervix, and uterus (Table III).

TABLE III. CHANGES IN THE WATER CONTENT AND DEGREE OF DEPOLYMERIZATION OF THE GROUND SUBSTANCE OF THE REPRODUCTIVE TRACT FOLLOWING TREATMENT WITH STILBESTROL AND RELAXIN

TREATMENT	REACTION	TISSUES		
		VULVA	CERVIX	UTERUS
None	% H_2O	77.1	79.9	80.0
Stilbestrol	% H_2O	84.0	85.3	85.2
Stilbestrol and relaxin	% H_2O	87.2	86.0	86.3
Stilbestrol	Depolymerization	Slight	Slight	None to slight
Stilbestrol and relaxin	Depolymerization	Good	Good	Good

Comment

The present results tend to confirm the concept that relaxin is a hormone of pregnancy and establish an action for relaxin in the sow quite analogous to the separation or relaxation of the pubic symphysis of the guinea pig. In this instance a marked dilatation of the uterine cervix of the sow is noted following treatment with relaxin. In both instances the action of relaxin requires pretreatment with an estrogen and in both instances the phenomenon is one concerned with parturition and specifically with the passage of the young. It is of further interest to note that the reaction involves the connective tissue primarily and acts in part by a depolymerization of the ground substance leading to an increased water content. The grossly edematous appearance of the tissues (vulva, cervix, and uterus) was confirmed by measurements of their water content. It is premature to speculate at this time on the mechanism involved but it is entirely possible that the cervical dilatation is a passive reaction due to changes in solubility of the ground substance and that loss of tonus occurred following depolymerization and influx of water. This would then allow the passage of large objects.

Conclusions

1. Relaxin causes a dilatation of the uterine cervix of the sow.

2. An increase in water content and degree of depolymerization of the ground substance of the uterus, cervix, and vulva is seen following treatment with relaxin.

3. The possible mode of action is discussed and the phenomenon compared with relaxation of the pubic symphysis.

References

1. Hisaw, F. L.: Proc. Soc. Exper. Biol. & Med. **23**: 661, 1926.
2. Fevold, H. L., Hisaw, F. L., and Meyer, R. K.: Proc. Soc. Exper. Biol. & Med. **27**: 604, 1930.
3. Fevold, H. L., Hisaw, F. L., and Meyer, R. K.: J. Am. Chem. Soc. **52**: 3340, 1930.
4. Hisaw, F. L., Fevold, H. L., and Meyer, R. K.: Physiol. Zool. **3**: 135, 1930.
5. Abramowitz, A. A., Money, W. L., Zarrow, M. X., Talmage, R. V. N., Kleinholz, L. H., and Hisaw, F. L.: Endocrinology **34**: 103, 1944.

6. Frieden, E. H., and Hisaw, F. L.: In Pincus, G., editor: Recent Progress in Hormone Research, Vol. VIII, New York, 1953, Academic Press.
7. Marder, S. N., and Money, W. L.: Endocrinology **34**: 115, 1944.
8. Zarrow, M. X.: Proc. Soc. Exper. Biol. & Med. **66**: 489, 1947.
9. Hisaw, F. L., and Zarrow, M. X.: Proc. Soc. Exper. Biol. & Med. **69**: 395, 1948.
10. Zarrow, M. X., and Rosenberg, B.: Endocrinology **53**: 593, 1953.
11. Zarrow, M. X., Holmstrom, E. G., and Salhanick, H. A.: J. Clin. Endocrinol. **15**: 22, 1955.
12. Hisaw, F. L., and Zarrow, M. X.: In Harris, R. S., and Thimann, K. V., editors: Vitamins and Hormones, New York, 1951, Academic Press, vol. 8, p. 151.
13. Graham, E. F., and Dracy, A. E.: J. Dairy Sc. **36**: 772, 1953.
14. Zarrow, M. X., Sikes, D., and Neher, G. M.: Am. J. Physiol. **179**: 687, 1954.
15. Zarrow, M. X., and Money, W. L.: J. Pharmacol. & Exper. Therap. **93**: 180, 1948.
16. Perl, E., and Catchpole, H. R.: Arch. Path. **50**: 233, 1950.

EFFECTS OF VITAMIN DEFICIENCIES ON FERTILITY, COURSE OF PREGNANCY, AND EMBRYONIC DEVELOPMENT IN RATS

HILDE PFALTZ, M.D.,* BASLE, SWITZERLAND, AND ELMER L. SEVERINGHAUS, M.D.,** NUTLEY, N. J.

SINCE most vitamins are involved in metabolic regulation they are important in growth processes. Vitamin deficiency is seen particularly in organs with active metabolism, which is characteristic of pregnancy. If vitamin requirements are inadequate for prolonged periods in experimental animals, disturbances of fertility, abnormalities of pregnancy, and maldevelopment of embryos have been reported. Evans and Bishop[4] called attention to some of these relationships. Hale[14, 15, 16] was the first to note in paired experiments on littermates, with and without vitamin A added to the diet, that microphthalmia, anophthalmia, jaw deformities, and harelip resulted from deficiency of A rather than from genetic factors. Warkany and his collaborators[38-43] have pursued this field with other vitamins as well. They have demonstrated skeletal anomalies with various deficient diets. Deficiency of vitamin A led to eye defects and abnormality of urogenital tract epithelium in the young.[44-47] Mandibular malformations followed riboflavin deficiency.[41-45] Confirmatory reports have been published by numerous other investigators.[6, 7, 9-12, 22, 34, 36]

The studies reported here concern the effects of deficiencies of thiamine, riboflavin, pyridoxine, and pantothenic acid individually on fertility, the course of pregnancy, development of the embryos, and the postnatal growth of the litters in rats. An extended account of these findings has been published in French and German.[50]

Vitamin requirements appear to be increased during pregnancy.[13, 28-32] Under certain circumstances synthesis of some of the vitamins is possible in various animals.[17, 20, 21, 24, 25, 51] To avoid uncertainties on this subject, we have provided the individual vitamins in ten times the amounts we had found adequate in earlier experiments in growing rats.[35] The vitamin supplements listed in Table I were mixed with sugar and fed to the animals individually in small dishes, from which they quickly devoured the vitamins. The basic vitamin-free diet is given in Table II, the salt mixture in Table III.

The animals were from a Wistar strain maintained in this laboratory for the past 20 years with no evidence of deterioration and without abnormalities such as those to be described. This report is based upon use of 2,600 adult females, vigorous and healthy individuals only. Two control groups were employed: one group received natural mixed rations, the other was fed the purified diet plus the entire vitamin supplement. The experimental groups had this same purified diet, but a single vitamin was omitted according to the following scheme.

*Medical Department, Hoffmann-La Roche, Inc., Basle, Switzerland.
**Vice President for Clinical Research, Hoffmann-La Roche, Inc., Nutley, N. J.

TABLE I. VITAMIN SUPPLEMENTS

PER DAY	PER WEEK
100 γ thiamine	100 I.U. vitamin A
200-400 γ riboflavin*	40 I.U. calciferol
200 γ pyridoxine	200 γ dl-alpha-tocopherol
500 γ pantothenic acid	40 mg. choline chloride
1000 γ nicotinic acid amide	
Once during pregnancy the animals were given 15,000 units vitamin K intramuscularly	

*Four hundred γ riboflavin corresponds to 20 times the amount required by the growing rat. This dose was followed only in the first experiments, subsequently 10 times the amount or 200 was equally effective.

TABLE II. BASIC DIET

Extracted casein	26%
Rice starch	56%
Cocoa fat, heated and aerated for 8 hours	13%
Salt mixture "Roche"	5%
	100%

TABLE III. SALT MIXTURE "ROCHE"

Sodium chloride	5 Gm.
Calcium lactate	35 Gm.
Calcium phosphate (tri)	15 Gm.
Ferric citrate	3.21 Gm.
Potassium iodide	.09 Gm.
Copper sulfate	.03 Gm.
Magnesium sulfate	5.5 Gm.
Potassium phosphate	26.53 Gm.
Sodium phosphate	9.6 Gm.
Zinc carbonate	.02 Gm.
Manganese sulfate	.02 Gm.
Sodium fluoride	.003 Gm.
	100.003 Gm.

The use of the purified diet with supplemental vitamins, but omitting the single vitamin to be tested, was begun either 13, 28, or 35 days before mating. The 13 day period was the usual one, except where noted in protocols. Group 1 then received the missing vitamin also from the day of mating to the termination of the experiment. Group 2 received this same vitamin beginning 13 days after mating. Group 3 received this vitamin beginning after parturition. Group 4 continued without the vitamin to be studied. One third of each group was continued with weight determined daily. Another third was employed to provide for sacrifice of two animals on alternate days, for macroscopic examination of ovaries and uteri, with photographs. The final third of each group was likewise sacrificed on alternate days for histologic examination of pituitary, ovaries, and uteri with embryos. These latter studies are still in progress.

The males employed for mating were maintained on natural rations, and were placed in the cages with females for 2 or 3 nights during pro-estrus or estrus.

Results

Fertility of female rats falls with increasing duration of deficiency of each of the four water-soluble vitamins prior to mating, as shown in Table IV.

Complete sterility followed 28 or 35 day deficiencies, with significantly lowered rates of conception after only 13 days' withholding of the vitamins. The results appear statistically significant (Chi square test).

TABLE IV. FERTILITY OF FEMALE RATS UPON WITHDRAWAL OF ONE VITAMIN

	BEGINNING OF DEFICIENT DIET FEEDING					
	35 DAYS BEFORE MATING		28 DAYS BEFORE MATING		13 DAYS BEFORE MATING	
VITAMIN WITHDRAWN	NUMBER OF ANIMALS	PER CENT BECOMING PREGNANT	NUMBER OF ANIMALS	PER CENT BECOMING PREGNANT	NUMBER OF ANIMALS	PER CENT BECOMING PREGNANT
Thiamine	20	0	20	0	40	17
Riboflavin	20	0	20	0	60	45
Pyridoxine	20	0	20	0	60	33
Pantothenic acid	20	0	20	0	30	47

CONTROL GROUPS*	NUMBER OF ANIMALS	PER CENT BECOMING PREGNANT
Purified diet plus vitamin supplement	20	75
Natural diet	40	80

*The two control groups are not significantly different ($P > 0.9$) and can be considered together. The differences in fertility from all other groups are statistically valid ($P < 0.01$). The differences between 13 day and 28 day deficient feeding are valid for riboflavin, pyridoxine, and pantothenic acid ($P < 0.01$), but less valid for thiamine ($P < 0.05$).

The course of pregnancy was followed by daily weights, which indicated fetal resorption or abortion. Since abortions tend to occur at night, with the fetuses being devoured, these accidents would be missed without daily weighing. The graphic records are divided to present data on animals going to term separately from those whose pregnancy was terminated spontaneously but prematurely. Fig. 1 presents data on thiamine deficiency in rats going to term. When the vitamin intake was restored after mating (Group 1) a rapid increase in weight of approximately 100 grams occurred during the pregnancy. The animals receiving the thiamine only from the thirteenth day of gestation forward showed a similarly rapid, but delayed, gain, amounting to about 40 grams each. In Groups 3 and 4, receiving no supplement of thiamine prior to delivery of young, the weight curves remained essentially flat.

For comparison, Fig. 2 presents data on animals kept under the same experimental conditions, but which did not give birth to live young. The Group 1 weight gain averaged only 28 grams although these animals received thiamine from the day of mating. The weight gains during only the first 8 days of gestation compare favorably with those of animals going to term. A slight gain occurred also in those animals of Group 2 that received thiamine from the 13th day of gestation. The clear differences in weight curves between the animals that went to term and those that lost the embryos earlier support the assumption that increase of weight is chiefly due to development of embryos.

Withholding of riboflavin is illustrated in Figs. 3 and 4. The weight gains induced by restoration of vitamin intake are less striking than for thiamine but the results are otherwise comparable. Perhaps maternal reserves of riboflavin are less quickly exhausted.

Results with pyridoxine deficiency are not shown in graphs, but were similar to those illustrated for thiamine. The results with pantothenic acid deficiency were not as striking as with the other three water-soluble vitamins.

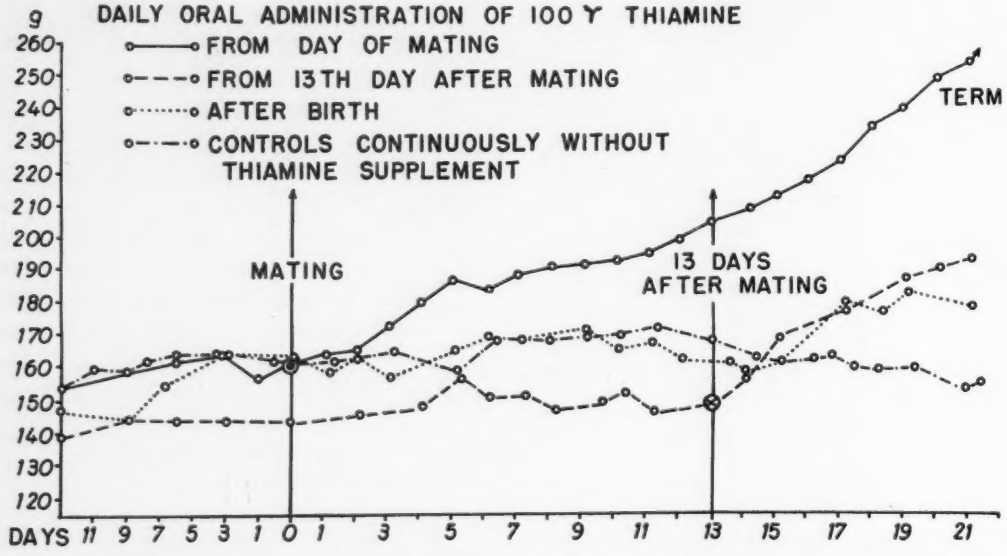


Fig. 1.—Average weights of rats giving birth, on diet without thiamine from thirteenth day prior to mating.

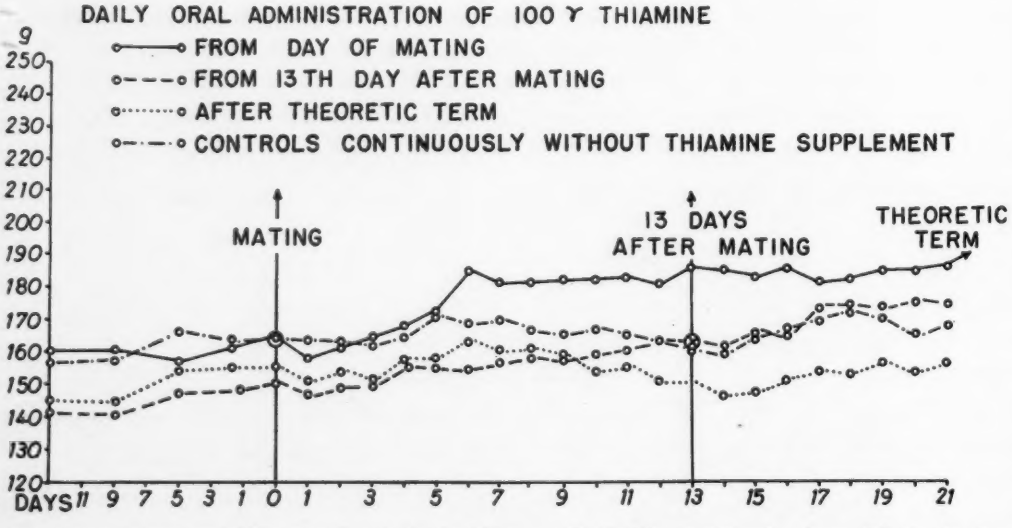


Fig. 2.—Average weights of rats not giving birth, on diet without thiamine from thirteenth day prior to mating.

The development of embryos is obviously dependent upon adequacy of maternal nutrition. Reduced numbers of embryos and inferior development are apparent on macroscopic examinations as early as the seventh day. In uteri obtained later in pregnancy, thickenings indicate the sites of resorption or abortion.

At times we observed edema and hemorrhages of the embryos as well as malformations. Statistical evaluation of the frequency of malformations is very difficult because malformation usually leads to abortion, sometimes to the mother killing the liveborn malformed infant, and in either case devouring the fetus. To avoid this handicap we sacrificed animals, especially in the third week of gestation, for macroscopic examination of fetuses. Thiamine-deficient

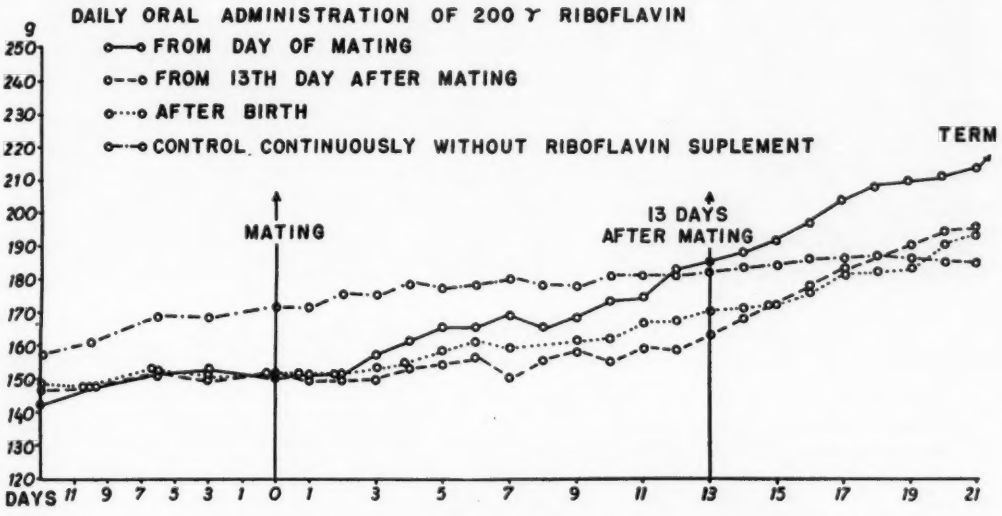


Fig. 3.—Average weights of rats giving birth, on diet without riboflavin from thirteenth day prior to mating.

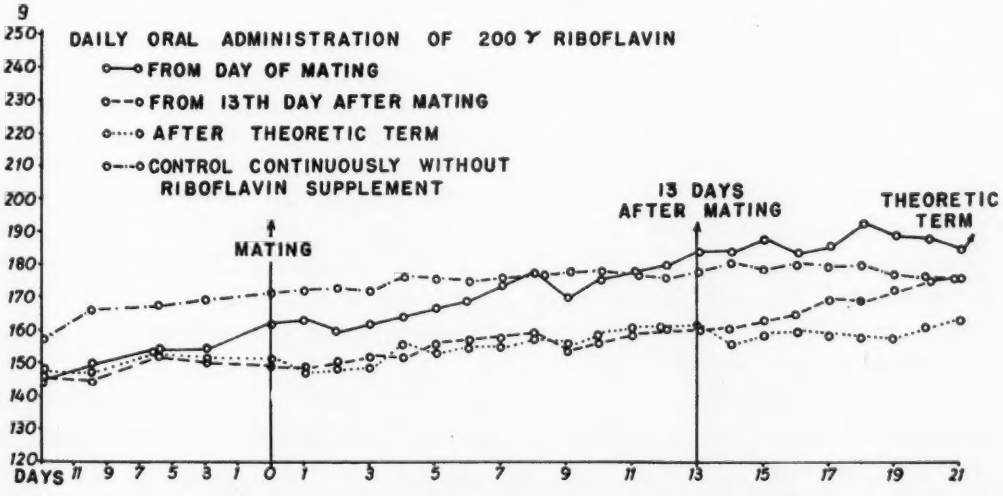


Fig. 4.—Average weights of rats not giving birth, on diet without riboflavin from thirteenth day prior to mating.

fetuses frequently showed hemorrhages about the head, edema of head and torso, delayed development with malformations, and sometimes exencephaly. Extensive hemorrhages were seen also after pyridoxine and pantothenic acid deficiencies. Following riboflavin deficiency, malformations and abnormalities

are strikingly frequent. No gross malformations were seen when the maternal intake of riboflavin was resumed at once after mating, but when the vitamin was omitted until the thirteenth day of gestation 23 per cent of the fetuses showed malformations, and omission of riboflavin throughout pregnancy in the other groups was followed by 41 to 43 per cent of young with malformations. The data are assembled in Table V. The percentages might well have been larger if we had routinely prepared cleared specimens to demonstrate skeletal anomalies. The living young produced by rats deficient in riboflavin until the thirteenth day of gestation show, as previously described by others,[7, 8, 19, 26] malformation of the jaw, as well as cleft palate, poorly developed mouth, and syndactylism (Figs. 5, 6, 7). Similar malformations have been seen in fetuses born of mothers with riboflavin deficiency prior to conception, but with vitamin supplied from the date of mating throughout gestation. The frequency and severity of abnormalities was reduced in such instances. The extent of the osseous malformations produced by riboflavin deficiency is illustrated by the cleared specimen reproduced in Fig. 8.[37]

TABLE V. DATA ON RESULTS OF RIBOFLAVIN DEFICIENCY

RIBOFLAVIN DEFICIENCY FROM 13TH DAY BEFORE MATING UNTIL	TOTAL NUMBER OF RATS	NUMBER OF RATS GIVING BIRTH	NUMBER OF YOUNG BORN	NUMBER OF YOUNG AT BIRTH WITH			NUMBER OF YOUNG		
				INJURIES	MALFORMATIONS		NORMAL AT BIRTH	STILLBORN	DIED IN FIRST WEEK OF LIFE
					NO.	%*			
Mating	20	14	108	68	0	0	38	2	58
13 days after mating	20	9	44	22	10	23	9	3	35
Day of birth of litter	20	7	41	19	17	41	5	5	36
End of experiment (end of lactation period)	20	11	37	17	16	43	3	1	36

*Calculated on the total number of young born.

Deficiency of pyridoxine or of pantothenic acid led to the production of only a few young, usually stillborn. Fetuses obtained by sacrifice in the third week of gestation commonly had subcutaneous hemorrhages on the head, back paws, or tail, and occasionally edema or such malformations as clubfoot or exencephaly. These abnormalities were seen seldom, and in very much milder forms, in animals produced by mothers who received the vitamin supplement beginning at once after mating.

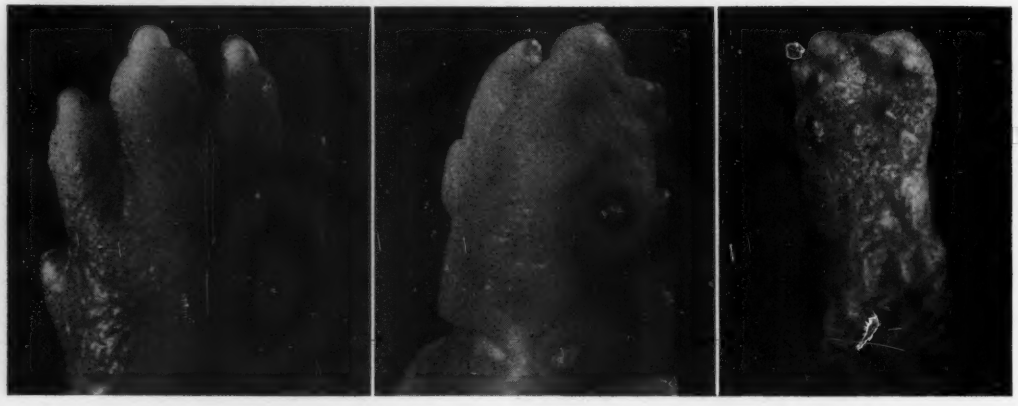
The condition of the young at birth and during lactation gave further evidence of the effects of vitamin deficiencies. Weight data are presented in Table VI, showing the range of weight from 6.0 grams average for the young born of mothers on natural rations down to 3.4 grams for the few animals born alive after maternal thiamine deficiency throughout gestation. The graded differences in duration of thiamine deficiency show clear differences in weight of newborn. The young of Group 1 (deficiency terminated at mating) were reared in part. A few litters from Group 2 (deficiency terminated on thirteenth day of gestation) were reared. In Groups 3 and 4, (deficient to term) all were stillborn or died within the 24 hours after birth. Furthermore, those

A. *B.*

Fig. 5.—*A*, Normal palate of newborn rat. The dam received vitamin supplemented diet. *B*, Cleft palate of a newborn rat; the dam received no riboflavin after the thirteenth day before mating.

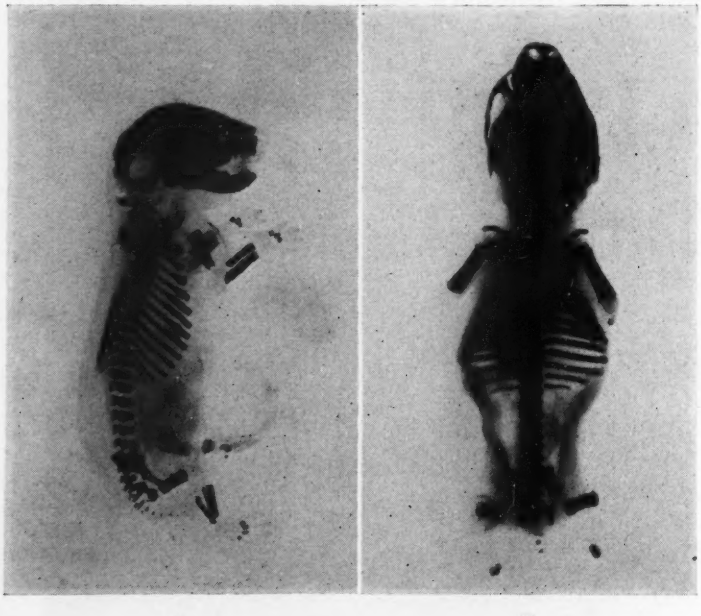
Fig. 6.—Newborn rat whose dam had received no riboflavin from thirteenth day before mating. Underdeveloped lower jaw, abnormal mouth formation, syndactylism.

young of Group 1 that survived were clearly retarded during their first two to three months, compared with control animals. After weaning, all animals were fed the completely supplemented diet. Those animals which survived to an age of 4 months had attained normal weight for age by that time. The weight data from experiments with deficiencies of riboflavin, pyridoxine, and pantothenic acid are similar to those for thiamine, although the weight handicap was numerically greater for thiamine.



A. *B.* *C.*

Fig. 7.—*A*, Normal paw of a newborn rat. *B*, Syndactylism. *C*, Absence of toes. The dams of *B* and *C* received no riboflavin after the thirteenth day before mating.



A. *B.*

Fig. 8.—Cleared specimens of newborn rats.
A, Normal. Dam received vitamin supplemented diet.
B, Dam deprived of riboflavin only, from 13 days prior to mating until 13 days after mating. Note absence of radius, ulna, carpals, tibia, fibula. Bones of feet and tail relatively incompletely formed.

The mortality of liveborn rats is obviously also dependent upon the duration of the vitamin deficiency in the maternal rats. These data are not tabulated.

TABLE VI. WEIGHTS OF NEWBORN RATS FROM MATERNAL ANIMALS FED VITAMIN-DEFICIENT DIETS

DIET	DURATION OF DIETARY DEFICIENCY: FROM THIRTEENTH DAY PRIOR TO MATING UNTIL: MATING (GROUP 1) NUMBER OF MATERNAL ANIMALS	NUMBER OF YOUNG	AVERAGE WEIGHT* OF NEWBORN (GRAMS)	13TH DAY AFTER MATING (GROUP 2) NUMBER OF MATERNAL ANIMALS	NUMBER OF YOUNG	AVERAGE WEIGHT* OF NEWBORN (GRAMS)	BIRTH OF LITTER (GROUP 3) OR END OF LACTATION PERIOD (GROUP 4) NUMBER OF MATERNAL ANIMALS	NUMBER OF YOUNG	AVERAGE WEIGHT* OF NEWBORN (GRAMS)
Purified diet and vitamin supplement with exception of:									
Thiamine	15	128	5.2	10	61	4.8	2	15	3.4‡
Riboflavin	7	53	4.6	8	40	4.4†	10	64	4.4†
Pyridoxine	8	75	5.4	13	51	4.9	3	16	4.2†
Pantothenic acid	13	75	5.0	10	79	4.5†	9	60	4.1‡

CONTROL GROUPS	NUMBER OF MATERNAL ANIMALS	NUMBER OF YOUNG	AVERAGE WEIGHT* OF NEWBORN (GRAMS)
Purified diet and vitamin supplement	13	95	5.0§
Natural diet	19	159	6.0‡

*Simple averages (i.e., not weighted) of average weight per litter; the weighted averages (i.e., calculated with consideration of number of young per litter) differ only insignificantly from the simple averages here reported.

†Difference from control group fed purified diet statistically slightly valid (P 0.05).

‡Difference from control group fed purified diet statistically valid (P 0.01).

§Differences from group fed with natural diet are totally valid (P 0.01).

There is an apparent difference between the newborn rats in the two control series. One series received the purified diet with vitamin supplements as described, the other received natural rations. The latter group showed superior birth weights and allowed rearing of more young, with more rapid postnatal growth. These and the other weight differences have been shown statistically significant by distribution analysis and use of the T test. It is obvious, therefore, that the purified diet with supplements employed is not truly a complete diet. No attempt was made to supply several other members of the B vitamin group.

Comment

The data presented indicate that reproductive function of female rats is impaired by vitamin deficiencies in several ways.

Fertility is distinctly lowered. Deficiency produced by removing, for 13 days before mating, any one of the four water-soluble vitamins studied produces a significant reduction in the rate of conception. Longer periods of deficiency led to complete sterility. In those animals which conceived after the 13 day deficit, fertility was further reduced by the smaller size of the litter. Although this effect may be based upon a smaller number of ova capable of fertilization, it is chiefly due to intrauterine fetal death, followed by resorption or abortion.

When pregnancies occur in deficient animals the disturbed fetal development can be seen by the reduced rate of weight gain of the pregnant animal. For similar single vitamin deficiencies during such short periods nonpregnant rats do not show significant weight handicaps. The flatter weight curves of

the pregnant rats are interpreted, therefore, as evidence of insufficient growth of the embryos due to vitamin deficiency. Addition of the missing vitamin during the pregnancy resulted in a steep rise in the weight curves, but normal values were not attained.

Vitamin deficiencies in the maternal animal affect the condition of the young even though they appear normal at birth. Birth weights are below those of control animals. Mortality within the first 24 hours is excessive. The surviving young are retarded in growth, attaining the same degree of development as the control young after several months. Ample supplements of vitamins to lactating rats do not prevent this postnatal handicap. This suggests that satisfaction of the vitamin need of the maternal rat is not achieved immediately by restoration of the missing vitamin. It is to be noted that depletion of the maternal organism also takes time. Examination of vitamin concentrations in milk suggests lower levels than those found in blood.

When vitamin supplementation is begun only during the last third of pregnancy, reversal of the injury to the fetus is partial at best. In spite of such restored vitamin intake the newborn show congenital abnormalities, reduced birth weight, and increased postnatal mortality.

The evidences of deficiency seen in the newborn, such as edema, hemorrhages, clubfeet, exencephaly, are nonspecific since they occurred after omission of each of the four vitamins studied. By contrast, cleft palate, underdevelopment of the mandible, and syndactylism appear to be specific evidences of riboflavin lack. It has been suggested by other investigators[15, 43] that the time during gestation when an injury occurs determines the malformation or abnormality subsequently seen. The damage may be by injury to the gamete during the vitamin deficiency prior to conception, or by injury to the fruit of conception in the early period of embryonic development. It appears that at some time in mesenchymal differentiation riboflavin deficiency can produce irreversible damage.

Skeletal or organ malformations have been described by Nelson and associates[27] and by Warkany[48, 49] following deficiency of other vitamins, notably folic acid and vitamin A. Our observations on vitamin A deficiency in rats show that there is, as expected, a much longer time required for depletion of the maternal animal than we have described above for the water-soluble vitamins.

The omission of one vitamin can lead to complex, though nonspecific, injuries and the harm cannot be prevented by ample supplementation with other vitamins, as already noted by others.[5, 18, 52] Increased metabolic needs of the pregnant rat include increased vitamin requirements. In an attempt to insure similar growth and development in comparison with normally fed animals, we have thought it necessary to use ten times the vitamin supplement we had previously found adequate for growing rats. Should one exceed by too great a margin the physiological requirement of certain vitamins, metabolic disturbances and injury to tissues may also occur. We have noted such findings in corroboration of findings previously reported.[1, 2, 23, 33] We believe the dosage of vitamins we have employed remains within the physiological range.

Summary

Experiments are reported on female rats fed a purified diet, adequate in protein, calories, and minerals, supplemented with water- and fat-soluble vitamins except for the individual vitamin being investigated. One of the four B vitamins, thiamine, riboflavin, pyridoxine, or pantothenic acid, was withheld from the animals for 35, 28, or 13 days before mating, and again supplied from the day of mating, or from the thirteenth day of gestation, or after birth of the young. In proportion to the duration of the deficiency there occurred decreased fertility, resorption or abortion, congenital malformations and serious abnormalities, and impaired growth of young.

The 2,600 females were weighed daily, from the thirteenth day before mating until delivery of young, or the sacrifice of selected animals. Lowered fertility is indicated by a reduced rate of weight gain. Fluctuations in the individual weight curves appear to mark resorption or abortion. Congenital abnormalities were most frequent in fetuses obtained during the third week or in newborn of animals deficient in riboflavin during pregnancy. Those young carried to term in spite of maternal deficiencies are below normal birth weight, frequently show serious injuries, have a high postnatal mortality, and can rarely be weaned.

Adequate supply of thiamine, riboflavin, pyridoxine, and pantothenic acid is necessary in rats to provide fertility, normal development of embryos, and the rearing of young through the weaning period.

References

1. von Drigalski, W.: Klin. Wchnschr. **12**: 308, 1933.
2. von Drigalski, W., and Laupmann, W.: Klin. Wchnschr. **12**: 1171, 1933.
3. Editorial: Brit. M. J. **2**: 436, 1953.
4. Evans, H. M., and Bishop, K. S.: Science **56**: 650, 1922.
5. Frank, A.: Monatsschr. Kinderh. **25**: 147, 1923.
6. Giroud, A., and Boisselot, J.: Arch. franç. pédiat. **4**: 1, 1947.
7. Giroud, A., and Boisselot, J.: Arch. franç. pédiat. **4**: 317, 1947.
8. Giroud, A.: Rev. stomatol. **49**: 378, 1948.
9. Giroud, A., Ettori, J., Lévi, G., and Boisselot, J.: Ztschr. Vitaminforsch. **21**: 261, 1949.
10. Giroud, A., Lévi, G., and Lefebvres-Boisselot, J.: Ztschr. Vitaminforsch. **22**: 308, 1950.
11. Giroud, A., and Lefebvres, J.: Compt. red. Soc. biol. **145**: 526, 1951.
12. Giroud, A.: Etude Néo-natales **1**: 13, 1952.
13. Guggisberg, H.: In Halban, J., editor: Biologie und Pathologie des Weibes, Berlin, 1942, Urban & Schwarzenberg, vol. 2, p. 1.
14. Hale, F.: J. Hered. **24**: 105, 1933.
15. Hale, F.: Am. J. Ophth. **18**: 1087, 1935.
16. Hale, F.: Texas J. Med. **33**: 228, 1937.
17. Hoekstra, W., Pope, A., and Phillips, P.: J. Nutrition **48**: 421, 1952.
18. Hopkins, G. F.: Brit. M. J. **2**: 691, 1923.
19. Houet, R., and Lecomte-Ramioul, S.: Ann. Paediat. **175**: 278, 1950.
20. Isherwood, F., Chen, Y. T., and Mapson, L. W.: Nature **171**: 348, 1953.
21. Isherwood, F.: Proc. Nutr. Soc. **12**: 335, 1953.
22. Lefebvres, J.: Ann. méd. **52**: 225, 1951.
23. Maddock, C. L., Wolbach, S. B., Maddock, S., and Jensen, D.: Federation Proc. **6**: 396, 1947.
24. McElroy, L.: J. Nutrition **20**: 527, 1940.
25. Monroe, R., Sauberlich, H., Comar, C., and Hood, S.: Proc. Soc. Exper. Biol. & Med. **80**: 250, 1952.
26. Nelson, M., Sulon, E., Becks, H., and Evans, H.: Proc. Soc. Exper. Biol. & Med. **66**: 631, 1947.
27. Nelson, M., Asling, C. W., and Evans, H.: Science **114**: 479, 1951.
28. Neuweiler, W.: Klin. Wchnschr. **14**: 1793, 1935.
29. Neuweiler, W.: Klin. Wchnschr. **16**: 1348, 1937.

30. Neuweiler, W.: Klin. Wchnschr. **17**: 296, 1938.
31. Neuweiler, W.: Klin. Wchnschr. **18**: 769, 1939.
32. Neuweiler, W.: Monatsschr. Geburtsh. u. Gynäk. **109**: 322, 1939.
33. Neuweiler, W.: Gynaecologia **130**: 363, 1950.
34. Noback, C. R., and Kupperman, H. S.: Proc. Soc. Exper. Biol. & Med. **57**: 183, 1944.
35. Pfaltz, H.: Ztschr. Vitaminforsch. **12**: 193, 1942.
36. Piccioni, V., and Bologna, U.: Clin. ostet. **51**: 173, 1949.
37. True, R. M.: Stain Technol. **21**: 107, 1946.
38. Warkany, J., and Nelson, R. C.: Science **92**: 383, 1940.
39. Warkany, J., and Nelson, R. C.: Anat. Rec. **79**: 83, 1941.
40. Warkany, J., and Nelson, R. C.: J. Nutrition **23**: 321, 1942.
41. Warkany, J., Nelson, R. C., and Schraffenberger, E.: J. Bone & Joint Surg. **25**: 261, 1943.
42. Warkany, J., Nelson, R. C., and Schraffenberger, E.: Am. J. Dis. Child. **65**: 882, 1943.
43. Warkany, J., and Schraffenberger, E.: Proc. Soc. Exper. Biol. & Med. **54**: 92, 1943.
44. Warkany, J., and Schraffenberger, E.: J. Nutrition **27**: 477, 1944.
45. Warkany, J., and Schraffenberger, E.: Proc. Soc. Exper. Biol. & Med. **57**: 49, 1944.
46. Warkany, J., and Schraffenberger, E.: Arch. Ophth. **35**: 150, 1946.
47. Warkany, J., and Roth, C. B.: J. Nutrition **35**: 1, 1948.
48. Warkany, J.: Nutrition Rev. **12**: 348, 1954.
49. Warkany, J.: Oesterr. Ztschr. Kinderh. **10**: 165, 1954.
50. de Watteville, Von H., Jürgens, R., and Pfaltz, H.. Schweiz. med. Wchnschr. **84**: 875, 1954.
51. Wegner, M., Booth, A., and Elvehjem, C.: Proc. Soc. Exper. Biol. & Med. **45**: 769, 1940.
52. Wendt, H., and Schröder, H.: Ztschr. Vitaminforsch. **4**: 206, 1935.
53. Wilson, J. G., and Warkany, J.: Proc. Soc. Exper. Biol. & Med. **64**: 419, 1947.

PLACENTA PREVIA*

A Critical Appraisal Based on a Thirty-five-year Study at Bellevue Hospital (1919-1954)

ARTHUR M. REICH, M.D., NEW YORK, N. Y.

(From the Obstetrical and Gynecological Service [Third Surgical Division], Bellevue Hospital, and the Department of Obstetrics and Gynecology, New York University College of Medicine)

THE obstetrician, perhaps more than any other group in the field of medicine, has today voluntarily imposed upon himself a strict accountability for an unfavorable result leading to a maternal or a perinatal death. Placenta previa, having blackened the pages of obstetrical history, demands a critical appraisal directed toward the errors in management which have contributed to the high death rate of past decades.

To what extent is maternal mortality preventable in placenta previa? To what extent is fetal or neonatal mortality in this condition preventable? Answers to some of these questions may be found by reviewing the results obtained in placenta previa at Bellevue Hospital over a 35 year period studied in two separate series, namely, an earlier one covering the years 1919 to 1941, as compared to a recent one based on the years, 1941 to 1954. In the latter series a constructive program was initiated in the management of cases, based on what we believe to be solid concepts, to eliminate some of the adverse results of the earlier series. Today, the infant should have nearly a 90 per cent chance of a favorable result, while until very recently a 50 to 60 per cent likelihood of an infant death in this complication was accepted without challenge.

As a foreword, it should be stated that the discussion is limited strictly to the condition which our service considers as constituting a placenta previa. Therefore, the presence of a succenturiate lobe, of a placenta membranacea, or a detached product of late abortion, in any of which conditions placental structure might by chance be present at the cervical internal os, does not qualify a case for inclusion in this series. Also, we have studiously avoided including in the placenta previa group the so-called low implantation of the placenta in which the placenta does not reach the area of the anatomical cervical internal os. Such cases should be designated as *premature separation* of a *low-implanted placenta.* In contrast to placenta previa, nidation does not produce an obstructing organ interfering with the descent of the fetus. Moreover, it is not found to be in the region of the dilating zone of the cervix. The need for differentiation of low implantation of the placenta from true placenta previa is imperative, as the management of the former should be conservative.

*Presented at a meeting of the Brooklyn Gynecological Society, May 18, 1955.

Data on the Series Studied

Incidence.—The study covering this report as shown in Table I includes all consecutive cases of placenta previa which were proved either by a vaginal examination, or at the time of cesarean section, to have had the placenta reaching the internal os.

It embraces the era covering the years 1919 to 1954. Among a total of 69,815 patients, placenta previa occurred in 310, an incidence of 0.44 per cent, or 1 in 225. A great range of incidence has been reported in the literature.[1] This may well be explained by the inclusion of cases which have not been positively identified, and in some series by the interpretation of a low-implanted placenta as a type of previa.

TABLE I. INCIDENCE OF PLACENTA PREVIA, OBSTETRICAL SERVICE, BELLEVUE HOSPITAL, 1919-1954

TOTAL DELIVERIES	PLACENTA PREVIA	RATIO	INCIDENCE %
69,891	310 (316 infants)	1:225	0.44

Parity.—Placenta previa was found to have been present nine times as frequently in multiparous women as in the primiparous, as indicated in Table II. The higher the gravidity, the greater the incidence, as demonstrated in our series in which 45 per cent of the multiparas had had five or more pregnancies.

TABLE II. PARITY IN 310 CASES OF PLACENTA PREVIA, 1919-1954

	NO.	%
Primigravidas	32	10.3
Multigravidas	278	89.7
Multiparity of v or more	120	(45% of multiparas)

Presentation.—Often a helpful diagnostic factor is the finding of an abnormal presentation (Table III). In this series the breech was found to have been presenting in over 14 per cent, and a transverse lie was found in 11.5 per cent, giving a combined total of abnormal presentation of 25.7 per cent. It is significant that on the general service this total is but 5.1 per cent. Such an abnormal presentation combined with an unusually high station of the presenting part should give a suspicion of the condition.

TABLE III. PRESENTATIONS AMONG 310 PATIENTS WITH PLACENTA PREVIA, 1919-1954

	PLACENTA PREVIA SERIES			GENERAL SERVICE	
	NO.	%		%	
Vertex	208	73.2			
Breech	40	14.1	25.7	4.8	5.1
Transverse	33	11.6		0.3	
Face	3				
Unlisted	20				
Twins	6	1.9		0.98	

Type.—The classification of types of placenta previa in this series by number and percentage is listed in Table IV. The classification of a given case, whether it be lateral or marginal, partial, central, complete, total, incomplete, is not considered on our service as being very significant. These classifications represent statistical illusions because in the same patient the findings may vary

according to the time of examination, cases being perhaps successively diagnosed as marginal, partial, and finally central as labor advances. The significant fact is the presence of placenta previa and this finding alone, rather than the degree, should determine the steps of procedure. Prior to 1941, this dictum was not followed.

TABLE IV. TYPES OF PLACENTA PREVIA, 1919-1954

	NO.	%
Marginal	109	35.2
Partial	98	31.6
Central	85	27.4
Type unlisted	18	5.8

Operative Procedures.—The method of procedure employed for the delivery of the patient with placenta previa during the 23 year period from 1919 to 1941, itemized in Table V, affords a vivid picture of management of the patient during those years. The patient was submitted to a multiplicity of operative steps which were traumatic and productive of a material increase in blood loss. The induction of labor was performed without hesitancy and with little consideration for the period of gestation. The expectant plan of treatment was not practiced and the vaginal examination was performed without precautionary measures; its use was untimely as well as abused.

TABLE V. TYPE OF PROCEDURE FOR DELIVERY IN PLACENTA PREVIA

*Early Series, 1919-1941**

	NO.	%
Major Classification of Manner of Delivery.—		
Delivered by the pelvic route	160	81.6
Delivered by cesarean section	32	16.3
Maternal death undelivered	4	
Detail of Special Procedures.—		
Internal podalic version and breech extraction in a vertex or transverse	88	
Voorhees bags	83	
Induction of labor	68	
Artificial rupture of membranes in a vertex	22	
Artificial rupture of membranes in a breech	8	
Bag and/or pack and/or manual dilatation of cervix, in a breech	18	
Packing prior to delivery	17	
Manual dilatation of cervix, in a vertex	4	
Vaginal hysterotomy	1	

*Cases in this series: mothers, 196; infants, 199.

TABLE VI. TYPE OF PROCEDURE FOR DELIVERY IN PLACENTA PREVIA

*Recent Series, 1941-1954**

	NO.	%
Major Classification of Manner of Delivery.—		
Delivered by cesarean section	96	85
Delivered by the pelvic route	17	15
Maternal death undelivered	1	
Detail of Special Procedures.—		
Internal podalic version and breech extraction	2	
Spontaneous face presentation	2	
Artificial rupture of membranes, spontaneous vertex	3	
Artificial rupture of membranes, breech	10	

*Cases in this series: mothers, 114; infants, 117.

Nearly 82 per cent of the births in the early series were accomplished through the vaginal route, while only 16 per cent were by the cesarean method. The contrast with the route of delivery employed since 1941 to date, as noted in Table VI, becomes striking, inasmuch as nearly 85 per cent of these patients had cesarean sections, while but 15 per cent were delivered by the pelvic route.

TABLE VII. CESAREAN SECTION IN PLACENTA PREVIA

Recent Series, 1941-1954

	NO.	%
Patients sectioned	96	85
Parity.—		
Primiparas	16	
Multiparas	80	
Type of Previa.—		
Marginal	24	
Partial	32	
Central	37	
Unlisted	3	
Presentation.—		
Vertex	67	
Breech	6	
Transverse	19	
Twins	3	
Unlisted	1	
Time of Section.—		
Before onset of labor	61	
After onset of labor	35	
Type of Operation.—		
Classical	15	
Low flap	81	
Anesthesia.—		
General	56	
Regional, local	12	
Spinal	24	
Unlisted	4	
Uteri packed	14	
Maternal Results.—		
Mortality:		
Living	95	
Dead	1	
Morbidity*:		
Febrile	24	
Afebrile	72	
Infant Results.—		
Age of Fetus:		
Term	49	
Premature	43	
Early premature (28 to 32 weeks)	4	
Before twenty-eighth week	3	
Mortality:		
Living	82	
Stillborn	9	
Neonatal death	8	
Uncorrected mortality	17	17.2
Corrected mortality†	10	10.1

*Morbidity, a temperature of 100° F. on any day after the first 72 hours.
†Deduction allowed for (a) nonviability; (b) no fetal heart tone on admission.

At this point a parenthetical comment may be made on the place of cesarean section, as illustrated by the recent Bellevue Hospital series. The decision to perform a section was not based on parity, the type of previa, the presentation, or even the presence or absence of intrauterine life (Table VII). Cesarean section would indeed have been done in all the cases had it not been for special circumstances present in individual cases, such as onset of labor in a very early period of gestation, an error in diagnosis, delay in obtaining an operating room, or because of the advanced stage of labor on admission. The corrected infant mortality of 10.1 per cent in the cases so treated is very good when compared with that of other procedures.

Transfusions.—The patient with a placenta previa should at all times be protected by an attempt to maintain her cell volume at as near a normal value as possible. This should be secured for her by having suitably dated cross-matched compatible blood continuously available. In the event of a sudden profuse hemorrhage with shock, large volumes of blood given under pressure, with at times the use of additional blood channels, may be lifesaving.

During the earlier series, 1919 to 1941, due mainly to the difficulties encountered in obtaining blood, the number of transfusions administered was relatively low (Table VIII). This neglect was undoubtedly a factor in the poor results of the earlier as compared with the later series.

TABLE VIII. TRANSFUSIONS ADMINISTERED: EARLIER SERIES, 1919-1941, COMPARED WITH RECENT SERIES, 1941-1954

	TOTAL NO. OF PATIENTS	NO. TRANSFUSED	% TRANSFUSED
1919-1941	196	71	36.2
1941-1954	114	97	85.0

Puerperal Infection.—The table on puerperal febrile morbidity (Table IX), employing the rigid standard of rise to or above 100° F. in any 24 hours after the first day following vaginal delivery and after the 72 hour period in patients delivered by section, demonstrates the vulnerability of the placenta previa patient to puerperal infection. This is to be explained because of the location of the placental site so exposed to exogenous organisms. The resultant anemia and the traumatization of the friable cervical structures increase the likelihood of puerperal infection. For the prevention or the reduction of the puerperal infection in placenta previa, vaginal and rectal examinations should be avoided as much as possible, the normal cell volume maintained or promptly restored, cesarean section usually employed, and antibiotic and chemotherapy agents given prophylactically.

TABLE IX. POSTPARTAL, POSTOPERATIVE MORBIDITY: EARLIER SERIES, 1919-1941, COMPARED WITH RECENT SERIES, 1941-1954

	TOTAL NO. OF PATIENTS	NO. MORBID*	% MORBID
1919-1941	181	75	41.4
1941-1954	113	29	25.7

*Morbid.—Vaginal delivery: a temperature of 100° F. on any day after the first 24 hours. Cesarean section: a temperature of 100° F. on any day after the first 72 hours.

Massive Hemorrhage and Shock.—The state of shock presents great hazards to both infant and mother. An episode of vaginal bleeding serves as a warning signal in placenta previa. Several episodes of profuse bleeding occurring in a comparatively short space of time may produce severe shock. The fetus in

utero in a patient with this complication is subjected to variable degrees of anoxia with depression of the vital centers. With the patient in labor progressive detachments of placental cotyledons add progressively to the fetal hazards.

During the period 1919 to 1941, 25 per cent of the group developed a state of shock (Table X). Some of these were in shock because of delay in reporting to the hospital, perhaps after repeated vaginal examinations and unsuccessful procedures performed at home in attempting to arrest the bleeding. After admission, a still larger group developed shock either during attempts at induction of labor, or as a result of vaginal examination, or in the course of labor and its operative procedures.

TABLE X. THE OCCURRENCE OF SHOCK IN PLACENTA PREVIA

	TOTAL NO. OF CASES OF PLACENTA PREVIA	FREQUENCY OF SHOCK		TIME OF APPEARANCE OF SHOCK			
				PRIOR TO LABOR	DURING LABOR	AFTER DELIVERY	
		NO.	PER CENT			NO.	PER CENT
Early series, 1919-1941	196	50	25.5	10	15	25	50
In cases of maternal death	22	19	86.4	2	3	14	73.7
Recent series, 1941-1954	114	23	20.2	14	7	1	0.4
In cases of maternal death	2	1		1	0	0	0

The most striking observation made on this point in the study of the earlier series was that shock appeared in half of the patients during or after the third stage. Postpartum hemorrhage is to be expected in patients with placenta previa who are delivered per vaginam. This is the result of the trauma sustained by the exposed fragile and friable unprotected placental site. Twelve maternal deaths during these years were in patients delivered through the parturient canal, in all of whom the first appearance of shock occurred after the delivery.

In contrast, during the period covering the years 1941 to 1954, when the management of patients advisably avoided the vaginal examination in the labor or delivery rooms, as well as the traumatic effects of an induced labor, with frequent use of cesarean section, the total incidence of shock was reduced to 20 per cent. The outstanding difference in this latter series of patients, however, was the virtual elimination of the form of shock resulting from postpartum hemorrhage. The credit for this improvement seems to lie in the avoidance of delivery by the parturient canal.

It is instructive to note that, in the period from 1941 to 1954, bleeding profuse enough to produce a state of shock occurred in 10 patients, which could not be accounted for either by a vaginal examination, an operative procedure, or the processes of labor (Table XA). In four of this group massive hemorrhage occurred while the patients were under the expectant plan of treatment. This is contrary to the observations reported by Johnson.[2]

TABLE XA. OCCURRENCE OF SHOCK WITHOUT VAGINAL OR RECTAL EXAMINATION, ONSET OF LABOR, OR OPERATIVE PROCEDURE, 1941-1954

In a case of maternal death 11 minutes after admission	1
Patients admitted in shock	5
Occurrence after admission	4
Total cases	10

General Comments on Mortality From Placenta Previa.—A survey of the period included in the years from 1919 to 1941 gives at once the grim picture of the mortality to both mother and infant.[3] Eleven out of every 100 women lost their lives and nearly 55 in every 100 infants were lost.

The study of the placenta previa patients during the years 1941 to 1954 demonstrates the dramatic reduction in the maternal and perinatal mortality which can be accomplished by strict conformity to modern principles of management.

Perinatal Mortality.—Tables XI through XVII give the statistics on perinatal mortality in which the results during the years 1919-1941 are compared with those of the recent years 1941 to 1954. The tables are presented to show (a) the type of procedure employed to deliver the patients (Table XII); (b) the route utilized with its bearing on the outcome (Tables XIII and XIV): (c) the time of the occurrence of the stillbirths in reference to the patients' admission to the hospital, to the onset of labor, to its connection with the delivery processes, to the death of an undelivered mother (Table XV): (d) the period of gestation in cases of perinatal death (Table XVI).

TABLE XI. FETAL AND NEONATAL MORTALITY: EARLIER SERIES 1919-1941, COMPARED WITH RECENT SERIES, 1941-1954

	TOTAL NO. INFANTS	UNCORRECTED NO.	MORTALITY %	CORRECTED NO.	MORTALITY* %
1919-1941	199	109	54.8	77	38.7
1941-1954	117	31	26.5	13	11.1

*Corrected for nonviable infants and those without a fetal heartbeat on admission.

Prior to 1941, as reported in Table XII, it was customary to manage the patients with placenta previa by employing various types of procedures leading to a vaginal delivery, cesarean section having been resorted to in only 16 per cent. Internal podalic version followed by breech extraction was the most frequent operation during at least the first half of the years 1919 to 1941. After 1934, the favored procedure was the extraovular Voorhees bag in vertex and breech presentations, to be followed by the artificial rupture of the membranes after the bag was expelled through the cervix. In the latter years of the series, the simple artificial rupture of the membranes was depended upon. The fetal and neonatal mortality figures are given with each method employed. A figure for a corrected mortality rate is also given to provide a true comparison for each method. Even in those early years, the comparatively favorable results with cesarean section are to be noted.

TABLE XII. STILLBIRTH AND NEONATAL MORTALITY ACCORDING TO TYPE OF PROCEDURE: EARLIER SERIES, 1919-1941

TYPE OF PROCEDURE	TOTAL	UNCORRECTED MORTALITY		CORRECTED MORTALITY	
		NO.	%	NO.	%
1. Internal podalic version in a vertex or transverse presentation	89	56	63	48	54
2. Induction of labor	68	38	56	31	45.6
3. Bag and/or pack and/or manual dilatation of cervix in a breech presentation	18	11	61	8	44.4
4. Breech delivery with artificial rupture of membranes	8	6	75	3	37.5
5. Bag and/or pack and/or manual dilatation of cervix in a vertex presentation	19	7	37	6	31.6
6. Vertex delivery with artificial rupture of membranes	23	13	56.5	7	30.4
7. Cesarean section	32	10	31.2	4	12.5

The relation of the route of delivery to the perinatal results during the period 1919 to 1941 is presented in Table XIII. Its revelations are tragic but instructive.

TABLE XIII. OUTCOME TO FETUS AND NEWBORN ACCORDING TO ROUTE OF DELIVERY

DELIVERY	TOTAL NO. INFANTS	% BY ROUTE OF DELIVERY	LIVING	STILL-BORN	NEO-NATAL DEATH	UNCORRECTED MORTALITY		CORRECTED MORTALITY*	
						NO.	%	NO.	%
Earlier Series, 1919-1941.—									
Vaginal	162	81.5	68	57	37	94	58	72	44.4
Cesarean section	32	16.1	22	5	5	10	31.2	4	12.5
Death undelivered	5	2.5	0	5	0	5	100	3	60
Total	199		90	67	42	109	54.8	79	39.7
Recent Series, 1941-1954.—									
Vaginal	17	14.5	4	10	3	13	76.5	3	17.6
Cesarean section	99	84.6	82	9	8	17	14.5	10	10.1
Death undelivered	1	0.85	0	1	0	1	100	0	0
Total	117		86	20	11	31	26.5	13	11.1

*Corrected for nonviable infants and those without fetal heart tones on admission.

Since 1941 patients with placenta previa have been managed with few exceptions according to new principles and the fetal and infant results have improved (Table XIII). During these years, delivery by section was performed in about 85 per cent of the cases. The fetal and neonatal survival rate in 99 infants delivered by section rose to 85 per cent, with a corrected mortality rate of only 10 per cent. Of the 10 infants that were lost, 3 were found by autopsy to have only prematurity as the primary cause of death.

Only 17 out of a total of 117 infants since 1941 have been delivered through the vaginal route and of these only 4 survived. The total of 13 deaths is, however, reducible to 3, when the usual corrections are made.

A comparison of the perinatal death rate in the series of 1919-1941 with that of the recent 1941-1954 series is convincing evidence of the advantages of the new principles of management. A 50 per cent reduction has been accomplished in the uncorrected mortality figures, with a 70 per cent reduction in the corrected mortality statistics.

TABLE XIV. TIME OF OCCURRENCE OF STILLBIRTHS: EARLIER SERIES, 1919-1941, COMPARED WITH RECENT SERIES, 1941-1954

PERIOD	TOTAL NO. OF INFANTS	TOTAL NO. OF STILLBIRTHS		CORRECTED INCIDENCE* OF STILLBIRTHS		TIME OF OCCURRENCE OF FETAL DEATHS				MATERNAL DEATH UNDELIVERED	
		NO.	%	NO.	%	PRIOR TO ADMISSION	AFTER ADMISSION, PRIOR TO LABOR	DURING LABOR, PRIOR TO DELIVERY	DURING DELIVERY PROCEDURE	PRIOR TO ADMISSION	AFTER ADMISSION
1919-1941	199	67	33.7	47	23.6	8	0	26	28	1	4
1941-1954	117	20	17.1	7	6.0	9	3	6	1	1	0

*Includes those with a viable infant or death after admission.

Table XIV presents the total number of stillbirths in both series, showing the time of occurrence of fetal death. In the later series the total number of stillbirths was reduced by approximately 50 per cent, while the reduction in

the figure for corrected mortality, 75 per cent, was even more striking. It is significant that, prior to 1941, the stillbirths happened mainly either during labor or at the actual time of delivery. Credit for salvaging the lives of these infants since 1941 must be given to the recognition of the danger involved to the fetus when labor was completed by the vaginal route and of the necessity of avoiding these dangers by performing cesarean section.

Table XV records the period of gestation in relation to fetal and neonatal deaths. During this 35 year period, the mortality was 100 per cent when the gestational age was 32 weeks or under, at the time of delivery. A possible explanation for this universally fatal outcome might be found in the histological deficiencies in the endometrium at the isthmus uteri, resulting in a corresponding deficiency of the basal decidua in the placenta previa. The expectant plan of treatment has provided a means of prolonging pregnancy and improving thereby the chances of survival of the infant. Unless unfavorable circumstances intervene, we should aim to carry the pregnancy to 36 weeks or beyond, the patient in the meantime being continuously hospitalized.

TABLE XV. STILLBIRTHS AND NEONATAL MORTALITY, SHOWING PERIOD OF GESTATION AT DELIVERY

PERIOD OF GESTATION	TOTAL NO. OF INFANTS	LIVING	STILL-BIRTHS	NEO-NATAL DEATHS	MORTALITY	
					NO.	%
Earlier Series, 1919-1941.—						
Nonviable						
Under 3 pounds, below 28 weeks	10	0	5	5	10	100
Early premature nonviable						
Under 3 pounds, 28-32 weeks	10	0	5	5	10	100
Early premature viable						
Over 3 pounds, 28-32 weeks	19	0	9	10	19	100
Premature						
32-38 weeks	97	54	27	16	43	44.3
Term	58	36	16	6	22	37.7
Mother died undelivered	5	0	5	0	5	100
Total	199	90	67	42	109	54.8
Corrected mortality					79	39.7
Recent Series, 1941-1954.—						
Nonviable						
Under 3 pounds, below 28 weeks	8	0	6	2	8	100
Early premature nonviable						
Under 3 pounds, 28-32 weeks	7	0	3	4	7	100
Early premature viable						
Over 3 pounds, 28-32 weeks	2	0	0	2	2	100
Premature						
32-38 weeks	57	49	5	3	8	14
Term	42	37	5	0	5	11.9
Mother died undelivered	1	0	1	0	1	100
Total	117	86	20	11	31	26.5
Corrected mortality					13	11.1

While it has been gratifying to observe the material reduction in perinatal mortality during the past 13 years at Bellevue in the placenta previa group, we cannot feel that we have achieved the goal of an irreducible minimum. In the cesarean group, for example, 5 of the 10 accountable infant deaths might not have occurred if there had been less delay in performing a section. Accountability for another death, a stillbirth, lay at the patient's door in her failing to report to the hospital promptly instead of allowing two hours to

pass while bleeding profusely at home. On the other hand, in 2 deaths among the sectioned group, prematurity was the primary cause of death found at autopsy and in these an expectant plan of treatment might have been successful in preventing an early premature birth.

Of a total of 17 patients delivered by the vaginal route, the corrected fetal mortality was 3 deaths. The advanced state of labor at the time of admission of the patient had precluded the possibility of arranging for a section in a few cases. In instances of a nonviable infant of a gestational age of under 26 weeks the pelvic route of delivery had been chosen by election, which accounts for the high uncorrected figure for the vaginal deliveries.

Maternal Mortality.—During the years 1919 to 1941, one in every 9 mothers with a placenta previa died, or a total of 22 of 196 patients. In recent years, 1941 to 1954, there were only 2 deaths among 114 patients, or a ratio of 1 in 57 (Table XVI). The circumstances under which these deaths occurred, especially in the earlier series are analyzed in Table XVII.

TABLE XVI. MATERNAL MORTALITY: EARLIER SERIES, 1919-1941, COMPARED WITH RECENT SERIES, 1941-1954

PERIOD COVERED	TOTAL NO. OF PATIENTS WITH PLACENTA PREVIA	MATERNAL DEATHS	MORTALITY %
1919-1941	196	22	11.3
1941-1954	114	2	1.75

The patients of the earlier series were delivered before the establishment of blood banks, prior to the use of antibiotics and chemotherapeutic agents, and before present-day improvement in anesthesia. The earlier cases suffered from errors in management which themselves led to critical situations. Notable were the delay of the patients in seeking admission to the hospital and the attempts of a physician to examine the patient. There was no understanding of the value of an expectant plan of treatment or of the danger resulting from the induction of labor or of the perils resulting from certain operative procedures. Finally, the hazard of labor itself in the presence of this complication, with the continued danger of an uncontrollable postpartum hemorrhage, was not fully understood.

TABLE XVII. ANALYSIS OF MATERNAL MORTALITY

Earlier Series, 1919-1941.—		
Died undelivered		4
In labor	3	
No labor	1	
Delivered by cesarean section		3
Breech delivery		14
Preceded by internal podalic version	13	
Delivered by low forceps		1
Total		22 of 196 patients
Recent Series, 1941-1954.—		
Died undelivered (not in labor)		1
Delivered by cesarean section		1
Total		2 of 114 patients

Only 2 maternal deaths occurred in the recent series. One was that of a woman admitted to the emergency ward in a condition of irreversible shock, who died eleven minutes after admission. She was an unregistered case, a

private patient of an outside physician, with a history of an earlier episode of bleeding two weeks before, at which time hospitalization was not recommended. She was found at home in a condition of shock, having had a massive hemorrhage of unknown duration. An ambulance brought her to another hospital, from which a transfer was made to Bellevue. After admission heroic measures, utilizing blood transfusion by way of more than one blood channel and given under pressure, were unsuccessful.

The second death occurred in a woman who had had a cesarean section. At the time of the operation a very large fibroid obstructing the entry into the uterus was removed with an ensuing massive hemorrhage. Rapid administration of blood, sufficient in amount for replacement of blood lost was carried out, but death occurred on the fifth postoperative day from causes which were not made clear at autopsy.

Management

The following considerations have guided the formulation of a plan of management in cases of placenta previa which has been in effect since 1941 at Bellevue Hospital. It is based on a factual appraisal of the material as presented in this communication. A material reduction in the perinatal and the maternal mortality was accomplished by conforming, in so far as possible, to the principles as presented in the ensuing discussion.

1. Greater emphasis should be attached to the diagnostic points. A classification of patients with bleeding of the generative tract into those considered as having either probable or positive placenta previa is a valuable measure. Such screening may be accomplished by taking into consideration the type of bleeding episodes and the various probable diagnostic abdominal signs which as a group are so pathognomonic of the condition. A plea should also be made for the use of x-ray according to such techniques as those described by Snow and Powell,[6] Dippel and Brown,[7, 8] Beck and Light,[9] Moir,[10] Ude and Urner,[11] Reid,[12, 13, 14] Sutton,[15] Stallworthy,[16] Macafee,[17] and others. Cystography, displacement methods, and especially soft-tissue placentography have been badly neglected through improper techniques and poor interpretation.

2. An unfavorable outcome has often been due to the delay of the patient in promptly reporting the very first sign of vaginal bleeding. Great emphasis should be placed on an instructive educational program to correct this failure.

3. The patient with a placenta previa should be afforded the protection of constant observation, preferably in the hospital and at rest in bed. All traumatic factors should be avoided, such as vaginal or rectal examinations, induction of labor, or pelvic operative manipulative procedures. Supportive measures aimed at correcting or restoring cell volumes should be carried out.

4. By enforcing the rule of early and continued hospitalization, one hopes to avoid the high incidence of premature termination of pregnancy, aiming to carry it to at least 36 weeks.

5. The occurrence of a massive hemorrhage or of repeated profuse episodes of bleeding indicates the need for prompt termination of pregnancy. The condition of shock should not delay the operative procedure beyond the time found to be necessary to administer blood transfusions.

6. All patients with potential or actual placenta previa should be protected by having at hand at least two units of compatible bank blood. Transfusion is begun promptly as soon as loss of blood or cell volume studies indicate it. Transfusion should be administered during any operative procedure. Antibiotic therapy is begun and continued during the early days of the postoperative period to avoid or combat puerperal infection.

7. The vaginal examination is utilized for its decisive value in diagnosis. The dangers from it are mostly overcome by restricting its use to the operating room at a time when the complete team is ready to start the operation with an infusion running and compatible blood at hand for transfusion.

8. The continuation of labor usually results in increasing hemorrhage, for the reasons stated. Promptness in its termination by cesarean section has avoided many maternal and infant difficulties.

9. Labor when completed by the pelvic route is likely to be followed by severe postpartum hemorrhage. This may be accounted for by several factors: (a) the placenta does not readily separate; (b) the lower segment lacks contractile and retractile muscular forces to control bleeding; (c) the fragile tissues tear easily; (d) the deficient decidual structure leads to a deficiency of thromboplastin.[4, 5]

10. The method of delivery advocated when the pregnancy is to be terminated, either before the onset of labor or after its beginning, is cesarean section. The operation has been shown to have a tremendous advantage in avoiding the many complications and in reducing the perinatal mortality. Convincing proof has been offered by our study that the hazards attached to the vaginal delivery, even when handled by the most conservative methods, are considerable, and the end results poor.[18]

11. Danger to the infant occurs when any measure for hemostasis is employed which depends on compression against the placenta, whether by various operative means or by the use of a fetal part. These are the equivalents of strangulation, resulting in a depressed and anoxic fetus.

12. To care for the anoxic and depressed newborn infant, resuscitative measures, including intubation, should be carefully and wisely utilized. Arrangements for immediate efficient care of the premature infant should have been instituted before the delivery of such an infant.

Conclusions

A digest of the results in 310 consecutive cases of placenta previa treated at Bellevue Hospital from 1919 to 1954 has been presented, with a view to determining to what extent preventive measures might modify or eliminate many of the hazards.

In the part of the series observed in the period from 1941 to 1954, new principles of management were in force. Their adoption has to a considerable measure met the challenge and eliminated some of the gravest dangers, thus securing for these patients a greater measure of safety.

Due acknowledgment for the establishment of the principles of management in the recent series as embodied in the contents of this presentation is to be credited to Dr. William E. Studdiford, the director of the department.

References

1. Caldera, R.: J. Obst. & Gynaec. Brit. Emp. **46**: 531, 1939.
2. Johnson, H. W.: AM. J. OBST. & GYNEC. **58**: 1336, 1950.
3. Dill, L. V., Sheffery, J. B., and Wilson, P., Jr.: AM. J. OBST. & GYNEC. **58**: 739, 1949.
4. Kistner, R. W., Hertig, A., and Reid, D.: Surg., Gynec. & Obst. **94**: 141, 1952.
5. Findley, D.: AM. J. OBST. & GYNEC. **61**: 856, 1951.
6. Snow, W., and Powell, A. B.: Am. J. Roentgenol. **31**: 37, 1934.
7. Dippel, A. L., and Brown, W. H.: Bull. Johns Hopkins Hosp. **66**: 90, 1940.
8. Dippel, A. L., and Brown, W. H.: AM. J. OBST. & GYNEC. **40**: 986, 1940.
9. Beck, A. C., and Light, F. P.: New York J. Med. **39**: 1678, 1939.
10. Moir, J. C.: AM. J. OBST. & GYNEC. **47**: 198, 1944.
11. Ude, W. H., and Urner, J. A.: AM. J. OBST. & GYNEC. **29**: 667, 1935.
12. Reid, F.: Brit. J. Radiol. **22**: 81, 1949.
13. Reid, F.: Brit. J. Radiol. **22**: 557, 1949.
14. Reid, F.: Brit. J. Radiol. **22**: 643, 1949.
15. Sutton, D.: Brit. J. Radiol. **25**: 320, 1952.
16. Stallworthy, J.: AM. J. OBST. & GYNEC. **61**: 720, 1951.
17. Macafee, G. H. G.: J. Obst. & Gynaec. Brit. Emp. **52**: 313, 1945.
18. Kimbrough, R., and Jones, B. D.: AM. J. OBST. & GYNEC. **55**: 496, 1948.

METHYL ERGONOVINE (METHERGINE) IN THE THIRD STAGE OF LABOR

ROBERT K. FERGUSON, M.D., AND DUNCAN E. REID, M.D., BOSTON, MASS.

(From the Department of Obstetrics, Harvard Medical School and the Boston Lying-in Hospital)

METHERGINE* (methyl ergonovine) was synthesized from isolysergic acid by Stoll and Hofmann.[1] In 1948 it was made available commercially as Methergine tartrate. Several reports[2-12] attest to the fact that Methergine is a safe drug and valuable in the management of the third stage of labor.

Methergine has been used in conjunction with other oxytocic drugs on the Boston Lying-in house service since late in 1952. The present study was undertaken to evaluate the effectiveness of Methergine as an oxytocic in the management of the third stage of labor by comparing a series of cases in which Methergine was used alone to a series of cases in which Pitocin was used in conjunction with Methergine or ergonovine.

Material

The patients in this report were delivered recently on the Boston Lying-in house service. In an attempt to estimate more accurately the blood loss, the patients in the "Methergine series," composed of 419 cases, were all delivered by one of us (R. K. F.), or the delivery was observed by him. The control series of 143 cases was selected at random from the ward service. No conscious attempt to select cases was made except that no cesarean sections are included. In both series the age distribution is not remarkable. A large percentage of the patients were gravida i and ii; however, the Methergine series includes two gravida xi (Table I).

TABLE I. PARITY

GRAVIDITY	METHERGINE	CONTROL
Primigravidas	166	53
Multigravidas	253	90

TABLE II. COMPLICATIONS OF PRESENT PREGNANCY

	METHERGINE	CONTROL
None	371	99
Allergic disease	0	0
Cardiac disease	10	5
Leiomyoma	0	0
Myomectomy	0	1
Pre-eclampsia	22	5
Rh negative with titer	2	4
Vaginal bleeding, cause undetermined	7	7
Previous cesarean section	0	2
Anemia	8	20

*The Methergine was supplied through the courtesy of Sandoz Pharmaceuticals.

The complications of pregnancy are listed in Table II. This list includes merely those items which are thought to be of interest for purposes of this paper.

Method

Most of the patients in both series were given Seconal, Thorazine, and scopolamine analgesia. Ninety-six patients in the Methergine series and 17 in the control series, mostly multiparas in extremely active labor on admission, were given intravenous scopolamine and Dilaudid. The patients with cardiac disease were medicated with intramuscular Demerol.

The majority of patients in both series received ether, nitrous oxide, and oxygen anesthesia. Thirty-seven (8.8 per cent) in the Methergine series and 23 (16 per cent) in the control series received low spinal anesthesia, often referred to as "saddle block." A few patients in each series received local, pudendal, or no anesthesia whatsoever. In the Methergine series the patients with a vertex presentation receiving inhalation anesthesia were given 0.2 mg. of Methergine intravenously when the infant's head was at "full crown" and in breech presentation the Methergine was administered when the shoulders were being delivered. Patients receiving regional anesthesia were given 0.2 mg. of Methergine as above, except that the medication was given by the intramuscular route. In the control series Pitocin (2 I.U. diluted to 2 c.c. with normal saline) was given intravenously with the birth of the anterior shoulder, and Methergine 0.2 mg. or ergonovine, $\frac{1}{320}$ grain, was given intramuscularly immediately after delivery of the placenta. In breech deliveries the Pitocin was given intravenously with delivery of the shoulders and the Methergine or ergonovine intramuscularly after delivery of the placenta. The types of delivery are summarized in Table III.

TABLE III. TYPE OF DELIVERY

DELIVERY	METHERGINE (%)	CONTROL (%)
Spontaneous	35.0	37.7
Low forceps	57.0	51.7
Breech	2.4	3.5
Version and extraction	0	0
Scanzoni maneuver	3.4	3.5
Manual rotation	0.8	1.3
Forceps rotation, arrested transverse	0.4	2.3
Twins	1.0	0

In the Methergine series 364 patients received the drug intravenously, and 55 received the drug by the intramuscular route. Seventy-four patients receiving intravenous medication and 17 patients receiving intramuscular medication were given Methergine maleate in place of Methergine tartrate. The Methergine was given, on the average, from 3 to 5 minutes before the birth of the infant.

Results

Blood pressure response to the oxytocic was evaluated from blood pressures taken on admission, when the patient was fully anesthetized, five minutes after the oxytocic was given, and one hour thereafter. In the Methergine group, of the 401 normotensive patients, 2 patients showed an elevation of between 70 and 79 mm. Hg systolic five minutes after Methergine; however, these patients were being delivered under light nitrous oxide and oxygen anesthesia and were actively engaged in the expulsive phase of birth. Their blood pressures were normal one hour post partum. There were 18 hyper-

tensive patients (blood pressure of 140/90 or above on admission) with one patient showing an elevation of between 30 and 39 mm. Hg systolic. All of these patients were back to admission levels within one hour after delivery. In the control series, 141 patients were normotensive and 2 were hypertensive. There were no significant elevations in either the normotensive or hypertensive patients. There was no significant difference between the response to Methergine maleate and tartrate.

Blood loss at delivery is as shown in Table IV. Three hundred forty-two (81 per cent) of the Methergine series had an estimated blood loss of 200 c.c. or less at delivery, while 72 (51 per cent) of the control group had a blood loss of 200 c.c. or less at delivery. In the Methergine series, 6 patients (1.4 per cent) had a blood loss which required one or more transfusions, while 3 (2 per cent) patients in the control series had sufficient hemorrhage to require transfusion. One patient in the Methergine series had an acute inversion of the uterus with an estimated blood loss of over 1,000 c.c. The inversion was attributed to overzealous efforts to deliver the placenta prior to separation. The uterus was immediately replaced vaginally and the patient was successfully treated for shock. In the Methergine series, 21 patients had postpartum uterine atony of some degree and a blood loss of less than 500 c.c. All but 5 responded well to additional Methergine; these 5 either required or were placed prophylactically on an intravenous Pitocin infusion. In the control series 4 patients were placed on an intravenous Pitocin infusion. There was no correlation between postpartum bleeding and the type of anesthesia used.

TABLE IV. BLOOD LOSS AT DELIVERY

VOLUME (C.C.)	METHERGINE (%)	CONTROL (%)
0-49	0.7	1.4
50-99	34.4	7.7
100-149	27.4	18.2
150-199	19.1	30.1
200-299	14.1	32.2
300-399	2.4	6.3
400-499	0.7	2.7
Over 500	1.2	1.4

The duration of the third stage of labor is itemized in Table V. Three hundred twenty-four (77 per cent) of the Methergine series had a third stage of 5 minutes or less, while 83 (57 per cent) of the control series fell into this category. There were 9 (2.1 per cent) retained placentas (a third stage of 1 hour or longer) in the Methergine group and 2 (1.4 per cent) in the control series.

TABLE V. DURATION OF THE THIRD STAGE OF LABOR

TIME	METHERGINE (%)	CONTROL (%)
0-59 seconds	3.3	0.7
60-119 seconds	6.4	2.8
120-179 seconds	15.3	8.3
3-5 minutes	52.3	46.2
6-10 minutes	14.3	25.2
10-15 minutes	4.3	10.5
15-30 minutes	2.0	3.5
30-45 minutes	0	1.4
Over one hour	2.1	1.4

In most instances delivery of the placenta was accomplished by the Brandt maneuver. In the Methergine series there were 10 placentas requiring manual separation, 6 because of failure to separate and 4 with partial separation accompanied by brisk bleeding. One patient in the Methergine series developed atony and required manual separation of the placenta and multiple transfusions; the bleeding was controlled by an intravenous Pitocin infusion and finally by packing of the uterus. In the control series 5 placentas were manually removed, 2 because of failure to separate and 3 with partial separation and significant brisk bleeding. In addition, 4 placentas in the Methergine series were "trapped," that is, they had separated but were retained in the uterine cavity, and had to be manually removed.

Six patients in the Methergine series had postdelivery bleeding in the recovery room with a loss of 200 c.c. or over. In all these patients the bleeding was well controlled with additional Methergine. No patients in the control series were recorded as having significant bleeding during the period spent in the recovery room.

In the Methergine series there were two cases of postpartum endometritis, one case of subinvolution, one case of retained secundines not requiring dilatation and curettage, and 3 cases of retained lochia, all of which were treated conservatively. One patient who entered with a blood pressure of 140/70 had no elevation at delivery, but one hour later had a blood pressure of 164/110. This patient was given one dose of magnesium sulfate, and her blood pressure returned to normal and remained there during the remainder of the postpartum stay. In the control series there were one case of postpartum endometritis, 5 cases of subinvolution, and 3 cases of hemorrhage after 24 hours, 2 of which required dilatation and curettage for retained secundines.

Summary and Conclusions

A series of 419 cases where Methergine was used exclusively for the management of the third stage of labor is compared to a series of 143 cases where Pitocin and Methergine or ergonovine was used.

No allergic reaction or untoward cardiovascular response was noted following the parenteral administration of Methergine. In summary, Methergine is a safe, effective oxytocic and when used alone resulted in a short third stage of labor and minimal blood loss at delivery.

References

1. Stoll, A., and Hofmann, A.: U. S. Patents, Nos. 2,265,207, and 2,265,217.
2. Kirchhof, A. C., Racely, C. S., Wilson, W. M., and David, N. A.: West. J. Surg. **52**: 197, 1944.
3. Roberts, P. C.: West. J. Surg. **52**: 380, 1944.
4. Brougher, J. C.: West. J. Surg. **52**: 276, 1945.
5. Tritsch, J. E., and Schneider, E.: AM. J. OBST. & GYNEC. **50**: 434, 1945.
6. Baskin, M. J., Harvey, E. L., and McEndoffer, D. M.: Rocky Mountain M. J. **44**: 208, 1947.
7. Gipstein, S. L.: AM. J. OBST. & GYNEC. **54**: 1065, 1947.
8. Williams, B. C.: Rocky Mountain M. J. **44**: 207, 1947.
9. Tritsch, J. E., Schneider, E., and Longworth, E. F.: New York J. Med. **48**: 293, 1948.
10. Priver, M. S., et al.: West. J. Surg. **57**: 586, 1949.
11. Schade, F. F., and Gernard, H. C.: AM. J. OBST. & GYNEC. **59**: 627, 1950.
12. Schade, F. F.: AM. J. OBST. & GYNEC. **61**: 188, 1951.

A STUDY OF THIRTY-EIGHT CASES OF HYDATIDIFORM MOLE AT THE PENNSYLVANIA HOSPITAL

PAUL E. STROUP, M.D., PHILADELPHIA, PA.

(From the Department of Obstetrics and Gynecology, Pennsylvania Hospital)

EVEN though hydatidiform mole was described as early as the sixth century by Aetius of Amida the evolution of knowledge concerning this entity has been extremely slow. No contributions of merit found their way into medical literature until the nineteenth century when Velpeau and Boivin described it as a disease of the chorion and Marchand brought to light the essential feature of trophoblastic proliferation. Today much is known about this peculiar lesion, but it is still one of the most difficult and confusing problems that the obstetrician-gynecologist has to manage.

The present study is designed to emphasize some of the clinical features and problems of management that are encountered in this disease.

During the years 1933 to 1955 there were thirty-eight cases of hydatidiform mole at the Pennsylvania Hospital. Seventeen of the cases occurred during the first eleven years of the study and twenty-one during the last eleven years. There were 56,580 deliveries in the 22 year period, or an incidence of one mole per 1,488 pregnancies. The reported frequency varies from 1:145 to 1:3,000.[6] The former figure applies particularly to certain countries in the Orient especially Malaya, China, and the Philippines. This relatively common incidence is thought to be related to the degree of parity of the women of these areas. Mueller and Lapp's[16] figures of 1:1,349 pregnancies at the Kings County Hospital, Brooklyn, agree fairly closely with ours, but probably the mean incidence is about 1:2,000 pregnancies.

TABLE I. PARITY OF PATIENTS WITH HYDATIDIFORM MOLE

PENNSYLVANIA HOSPITAL SERIES			NOVAK SERIES[20]		
PARA	NUMBER	PER CENT	PARA	NUMBER	PER CENT
0	11	29	0	38	34.5
i	14		i	27	
ii	6		ii	24	
iii	2		iii	4	
iv	1		iv	4	
v	0	71	v	5	65.5
vi	0		vi	3	
vii	3		vii	3	
viii	1		viii	1	
ix	0		ix	1	
			Unknown	10	
Total	38			120	

Mole is thought to be more frequent in multiparas and especially in women past the age of 40. As can be seen from Table I, 27, or 71 per cent, of our patients were multiparous. Seven of these patients had 3 or more children. Novak[20] reported 72, or 65.5 per cent, multiparous patients in 110 cases of

mole with only 21 who had had three or more children. The small number of patients of high parity in these two groups tends to detract from a correlation between degree of parity and incidence of mole.

The age span in the Pennsylvania Hospital series (Table II) was from 15 to 48 years, 63 per cent being between the ages of 20 and 30 and only 5 per cent over the age of 40. In Novak's[20] series 60 per cent* were between the ages of 20 and 30 years and 8 per cent over 40 years. Several cases occurring in patients past the age of 50[6, 15, 21] were recently reported, but this is relatively rare.

TABLE II. AGE INCIDENCE

PENNSYLVANIA HOSPITAL SERIES			NOVAK SERIES[20]		
YEARS	NUMBER	PER CENT	YEARS	NUMBER	PER CENT
Below 20	5	13.2	Below 20	20	16.8
20-30	24	63.1	20-30	71	59.7
31-40	7	18.4	31-40	19	15.9
41-50	2	5.3	41-50	7	5.9
Over 50	0	0.0	Over 50	2	1.7
			Unknown	1	

Seventy-one per cent of our patients who had moles were white. This is not significant in view of the fact that during the past 22 years 72 per cent of our obstetrical patients were white.

Neither could any statistical difference be found when comparing Jewish and non-Jewish patients. Five per cent of our mole patients were Jewish, but only 8 per cent of our obstetrical admissions during this interval were Jewish.

Similarly, there is no difference in the breakdown of private and ward mole patients, 40 and 60 per cent, respectively, when compared with 37 per cent private and 63 per cent ward obstetrical admissions.

Symptoms

Bleeding is almost a *sine qua non* for the diagnosis of hydatidiform mole, its onset being usually between the third and fifth months of gestation. In our series (Table III) only 31 per cent of the patients started to bleed between the third and fifth months. The majority, 51 per cent, began to bleed during the first or second month. Five patients had a history of constant spotting since the last normal menstrual period, and one had no bleeding until the seventh month. One patient had no bleeding and was admitted because of severe nausea and vomiting.

TABLE III. ONSET OF BLEEDING

GESTATION IN MONTHS	NUMBER	PER CENT
1	9	23.6
2	10	26.5
3	4	10.5
4	8	21.0
5	0	0.0
6	0	0.0
7	1	2.6
Constant spotting since last normal menstrual period	5	13.2
No bleeding	1	2.6

The duration of bleeding (Table IV) varied from one day to 4½ months. Seventy-six per cent of the patients bled for less than two months. No typical

*The percentage values have been rounded off for convenience of memory.

pattern of bleeding could be discerned. Bleeding was continuous in 69 per cent of the patients and intermittent in 31 per cent. In some cases only an intermittent or continuous brownish discharge was noted. In others intermittent or continuous bright red spotting was the rule. Intervals between episodes of spotting varied from a single day to several weeks. Hemorrhage, intermittent or terminal, punctuated the course of bleeding in many cases.

TABLE IV. DURATION OF BLEEDING

MONTHS	NUMBER	PER CENT
1	21	55.2
1-2	7	18.4
2-3	5	13.2
3-4	2	5.3
4	2	5.3
No bleeding	1	2.6

Perhaps an index of the amount of bleeding can be gained from hemoglobin values obtained on admission (Table V), 58 per cent of which were below 10.9 Gm. per cent, and the fact that the majority of patients required one or more transfusions before leaving the hospital.

TABLE V. HEMOGLOBIN VALUES ON ADMISSION

GM.	PER CENT	NUMBER
Less than 7.7	50	1
9.2	60	8
10.9	70	13
12.3	80	7
15.4	100	7
Not recorded		2

Pain as one of the components of the symptom complex of mole has about the same significance as in cases of threatened or inevitable abortion and usually precedes the passage of the mole by a few hours to several days.

Nausea and vomiting deserve more emphasis. Some degree of nausea or vomiting is found in 50 to 75 per cent of pregnant patients.[14, 24] About one-third of these patients require outpatient treatment and only an infrequent one requires hospitalization. Nausea and vomiting occurred in 22, or 58 per cent, of the mole patients, which is comparable to the incidence found in normal pregnancies. Eight of the 22 patients were recorded as having daily or severe nausea and vomiting, however. This finally necessitated admission in 3 of the cases. Of the 16 multiparous patients with moles who experienced nausea and vomiting, only 4 had had the same symptoms with former pregnancies and 4 with subsequent pregnancies.

Signs

Occasionally the clinical features of pre-eclampsia and eclampsia may be seen in a patient with hydatidiform mole. The onset and progression of hypertension, albuminuria, and fluid retention are frequently rapid and occur at an earlier time in pregnancy than usual.[22] Both ante- and postpartum convulsions have been recorded,[16] the latter being less frequent.

In this series only 13 patients had systolic blood pressures greater than 140 mm. Hg and/or diastolic pressures greater than 90 mm. Hg. Four of the 13 had associated albuminuria. The blood pressures in all patients but one returned to normal by the time they were discharged from the hospital. This one patient had obvious renal disease and had been admitted in congestive heart failure.

Abnormal size of the uterus is a frequent finding in molar pregnancies. Lull and Kimbrough[14] stated that in 50 per cent of the cases the uterus is larger than would be expected by gestational age. In the remainder it is either of normal size or smaller than would be expected. Jones,[11] however, stated that the uterus is usually smaller than would be expected.

In 18 per cent of our cases the uterus was smaller than or of a size compatible with the gestational age. In 13 per cent the size of the uterus was thought to be increased by 2 to 3 weeks over the calculated age, and in 53 per cent by 1 to 4 months. The remaining 16 per cent had already passed most of the mole before being admitted to the hospital, and therefore were difficult to evaluate. Frequently the increase in height of the uterus is prodigious, and it may change as much as 3 to 5 cm. in a week's time.

The presence of polycystic ovaries in association with hydatidiform mole has been variously reported. Eastman[5] gives the range of frequency as 25 to 60 per cent, Lull and Kimbrough[14] as approximately 50 per cent, and Novak,[18] quoting Cattalorda and Runge, as 59 and 16 per cent, respectively. In our series 16 per cent had enlarged cystic ovaries.

Acosta-Sison[1] has frequently stressed the importance of the softness and fullness of the lower uterine segment as a diagnostic sign in mole cases. This one feature has enabled her to diagnose successfully several cases preoperatively.

Finally, abdominal examination discloses the time-tested signs of absence of fetal parts, movement, and heart sounds and occasionally the presence of uterine contractions. Of course such signs are of value only in the larger moles.

Diagnosis

The diagnosis of hydatidiform mole is easy only if one has a high index of suspicion. Besides a consideration of the signs and symptoms previously discussed, there are certain diagnostic aids which are useful.

A flat film of the abdomen was of great importance in 8 cases of the present series. The usual report is that of a large soft-tissue mass with no evidence of a fetal skeleton. It must be remembered, however, that occasionally there will be no evidence of a fetal skeleton at a gestational age of 20 weeks and also that in multiple pregnancies the uterus may be quite large and yet show no fetal skeleton. The latter problem presented itself in the case described by Brody and Horowitz,[2] wherein the signs and symptoms were typical of mole but the final diagnosis was that of twin pregnancy.

Acosta-Sison[1] has described the use of a uterine sound to differentiate between hydatidiform mole and normal intrauterine pregnancy. In a molar pregnancy wherein the uterus is enlarged to the size of a 5 months' gestation the sound can be introduced far beyond the lower uterine segment. In a normal pregnancy of the same gestational age the sound would be arrested by membranes at the internal os. Obviously, this procedure is fraught with danger.

Of changing value in diagnostic import is the biological test for chorionic gonadotrophin. Formerly, it was thought that by determining the titer of chorionic gonadotrophin, one could differentiate between normal pregnancy and hydatidiform mole. Now it is recognized as being of limited importance, especially in the first trimester when the titer for a normal pregnancy may exceed that of a mole of the same age. After the first three months the titer in a single pregnancy drops markedly, whereas in a mole it will remain the same or rise. It must be remembered, however, that titers in multiple pregnancies are very high and tend to drop more slowly than in single pregnancies.

The difficulty in making a diagnosis of hydatidiform mole may be further emphasized by the varied diagnoses on admission in our cases. Six patients were admitted two or more times before the true nature of the condition was

established. There were 24 admissions for threatened abortion, 3 for severe nausea and vomiting of pregnancy, 1 for toxemia, 1 for an ovarian mass, 2 for missed abortion, and 16 for hydatidiform mole. Of the 16 patients admitted with the correct diagnosis, 10 passed some or all of the mole prior to or at the time of admission. If one excludes then the 10 cases in which tissue was passed, the correct diagnosis was made on admission only 16 per cent of the time. In 137 cases of mole reported by Acosta-Sison the correct diagnosis was arrived at in 28 per cent of the cases.

Treatment

Spontaneous Abortion.—Spontaneous abortion of the mole followed by thorough dilatation and curettage is the most satisfactory plan of therapy. Declining gonadotrophin titers may be of great value in indicating the moles that are likely to be aborted spontaneously or respond to Pitocin stimulation.

In 17 of our cases spontaneous abortion of the mole occurred either prior to or subsequent to admission. Eight of the 17, representing mostly patients who aborted in the hospital, were taken to the operating room for dilatation, evacuation, and packing of the uterine cavity. Two were later treated by hysterectomy, one because the mole was interpreted as being malignant and the other because of profuse vaginal bleeding, a strongly positive Friedman test, and uteroovarian enlargement. No evidence of malignancy was found in either case.

Abdominal Hysterotomy.—Abdominal hysterotomy is usually chosen when the plan of therapy just mentioned fails and the uterus is larger than a 12 weeks' gestation.

Four of the 38 cases were treated by abdominal hysterotomy. The preoperative diagnosis of hydatidiform mole was not entertained in two of them. The operative intentions were therapeutic abortion for intractable hyperemesis and resection of a rapidly enlarging ovarian cyst.

Hysterectomy.—Hysterectomy is generally reserved for the parous patient over 35 who has a large mole, because of the increased incidence of choriocarcinoma in older women.

Three of our 38 cases were treated by subtotal hysterectomy—one because of the patient's age and parity; one because of severe cardiovascular disease; and one because of toxemia and vaginal bleeding. In the last case the justification is difficult to understand.

TABLE VI. TREATMENT

OUTCOME OF MOLE	NUMBER PATIENTS	PATHOLOGICAL DIAGNOSIS	ADDITIONAL PROCEDURES*	FINAL PATHOLOGICAL DIAGNOSIS
Spontaneous abortion	17	Benign (16)	D & E (8)	Benign (17)
		Malignant (1)	TAH BSO (1)†	
			TAH BSO (1)	
Abdominal hysterotomy	4	Benign	0	Benign
Supravaginal hysterectomy	3	Benign	0	Benign
Dilatation and evacuation	14	Benign (11)	D & E‡ and TAH BSO (1)	Benign (12)
		Malignant (3)	TAH BSO (1)	Malignant (2)
			TAH (1)	

*TAH BSO = total abdominal hysterectomy and bilateral salpingo-oophorectomy.
†Clinical diagnosis of choriocarcinoma.
‡Curettings interpreted as choriocarcinoma.

Dilatation and Evacuation.—Dilatation and evacuation as a primary procedure is performed when the uterus is smaller than a 12 weeks' gestation. Fourteen of the cases in our series were treated in this fashion. Four deserve further comment:

B. G., a 40-year-old gravida iii, para ii, was admitted with the diagnosis of hydatidiform mole of 8 weeks' gestation. The pathological interpretation of the curettings was malignant hydatidiform mole (Fig. 1). Fifty-four days later a panhysterosalpingo-oophorectomy, performed because of continued vaginal bleeding and a rising gonadotrophin titer, confirmed this diagnosis (Fig. 2). The patient, when examined one year later, was living and well.

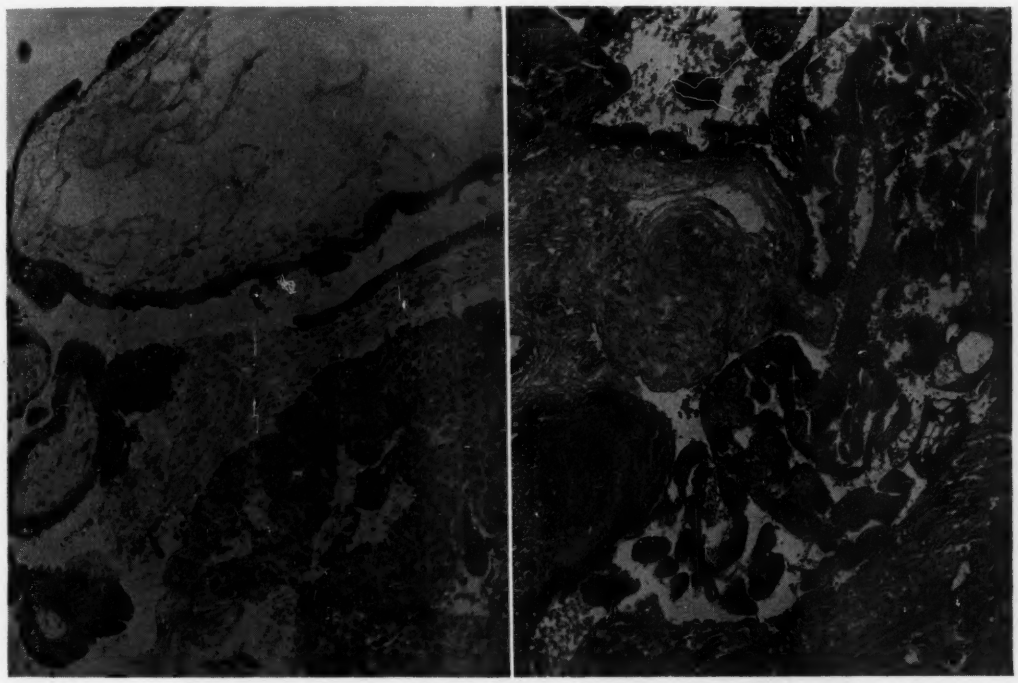


Fig. 1. Fig. 2.

Fig. 1.—Curettings of patient B. G., demonstrating hydatid villi and trophoblastic hyperplasia with normal and abnormal mitoses and hyperchromatic nuclei.

Fig. 2.—Section of the uterus of patient B. G., demonstrating deep myometrial invasion by villous and trophoblastic structures.

M. T., a 26-year-old gravida ii, para i, was admitted with a hydatidiform mole of 8 weeks' gestation. The pathological interpretation of the curettings was malignant hydatidiform mole. This patient was living and well, without further therapy, seven years later.

L. S., a 25-year-old gravida iii, para i, was admitted with the diagnosis of hydatidiform mole. Three curettages had been performed at another hospital. Curettings obtained at the Pennsylvania Hospital were interpreted as malignant hydatidiform mole (Figs. 3 and 4). Because of this, a total abdominal hysterectomy was performed which confirmed the diagnosis of malignant mole (Fig. 5). The patient was living and well seven months after operation.

D. D., a 23-year-old gravida iii, para ii, was admitted for profuse vaginal bleeding one month after curettage for benign hydatidiform mole. A repeat curettage was interpreted as choriocarcinoma, but subsequent hysterectomy showed only a uterus with residual benign molar tissue.

Time of Termination of Molar Pregnancy

The moles in our series terminated at various gestational ages. The interval from the onset of the molar pregnancy to the initial surgical procedure varied from one to seven months. The majority, 74 per cent, were interrupted between the third and fifth months. In the 94 cases of mole reported by Cabrera,[3] the gestational age at termination varied from one to seven months, 69 per cent of the cases ending between the third and fifth month.

TABLE VII. GESTATIONAL AGE OF MOLE AT TERMINATION

	MONTHS						
	1	2	3	4	5	6	7
Number of moles	4	2	9	13	6	2	2

Fig. 3.

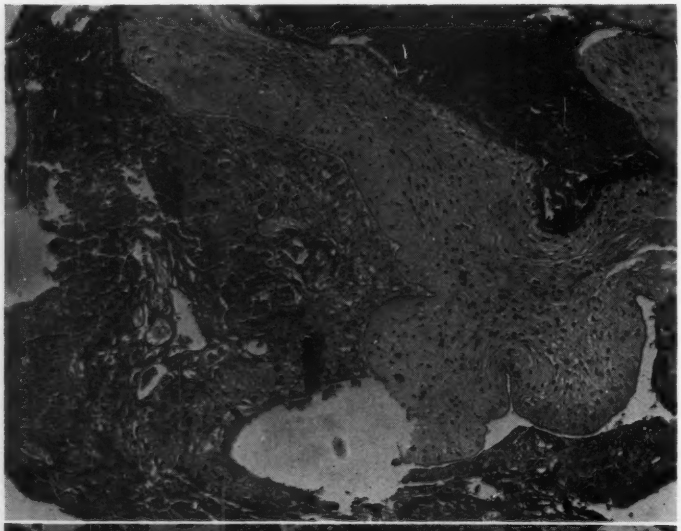


Fig. 4.

Fig. 3.—Curettings of patient L. S., demonstrating chorionic villi with masses of trophoblastic cells.

Fig. 4.—High-power view of Fig. 3 demonstrating plasmoditrophoblast and cytotrophoblast.

Follow-Up

Of the 38 patients no follow-up was available on 6. Eighteen were followed for 3 to 12 months, 2 for 2 years, and 12 for 3 or more years. The longest follow-up has been for 21 years. All the patients were living and well at the time they were last seen.

Eleven of the 38 patients (37 per cent) had a total of 14 postmolar normal pregnancies. In the 200 cases of mole reported by Hertig and Sheldon[9] there were 75 (37.5 per cent) subsequent normal pregnancies.

TABLE VIII. FOLLOW-UP

	DURATION OF FOLLOW-UP	NO. OF PATIENTS	SUBSEQUENT PREGNANCIES*
Living and well	3 months to 12 months	18	4
Living and well	2 years	2	1
Living and well	3 years	3	3
Living and well	4 years	4	3
Living and well	5 or more years	5	3
No follow-up		6	

*Does not include miscarriages.

Fig. 5.—Section of uterus of patient L. S., demonstrating deep myometrial invasion by villous and trophoblastic structures.

Gonadotrophin Studies.—Only 25 of the 38 cases had a follow-up with chorionic gonadotrophin studies. It is usually recommended that quantitative assays be performed every week until two consecutive negative tests have been obtained, then once monthly for from 6 to 12 months.

In 21 of the 25 cases, once the tests became negative, they remained so. The time interval from definitive therapy to the first negative assay varied from 4 days to 3 months. In 6 cases the tests were negative in less than 23 days, in 17 by one month, and in 21 by 3 months (Fig. 6). If one excludes the

4 patients in whom the tests did not remain negative, then 17, or 85 per cent, had negative assays by the end of two months. The results of the tests that did not remain negative could all be explained on the basis of either being false positives or residual hydatidiform tissue.

What of the assays that remain positive beyond two months? Provided renal function is normal, a slowly declining titer usually represents either dying trophoblast or the presence of large polycystic reservoirs of gonadotrophic hormone. A *rising* titer is of more significance, representing viable trophoblastic tissue in the decidual layer, a malignant mole, chorionepithelioma, or normal pregnancy.

Significance of Microscopic Findings.—Should the diagnosis of a malignant mole or chorionepithelioma from a mole specimen or curettings compel the clinician to do an immediate hysterectomy? Many authors[9, 10, 25] have attempted to establish criteria by which one could tell whether a certain mole would develop into choriocarcinoma or become massively invasive. Despite many scholarly treatises the problem is still unsolved, and one cannot point to any one or group of features that will definitely indicate whether a mole will pursue a benign or malignant course.

Possibility of Malignancy.—Since choriocarcinoma is such a rapidly metastasizing lesion, it is mandatory that the diagnosis be made and therapy be instituted immediately. Most authors agree that after a mole is evacuated the chance of malignancy is minimal if there is no further hemorrhage, the uterus involutes normally, and the pregnancy test becomes negative. If bleeding persists or recurs, especially in the presence of a subinvoluted uterus and positive pregnancy test, a thorough dilatation and curettage should be performed and a chest x-ray taken. The usual result of curettage is no trophoblastic tissue or trophoblastic tissue with villi. Novak[20] believes that hysterectomy following this curettage is warranted only if bleeding persists or the curettings show masses of trophoblast with no villi; even then, he stresses, one usually finds only residual molar tissue deep in the uterine wall.

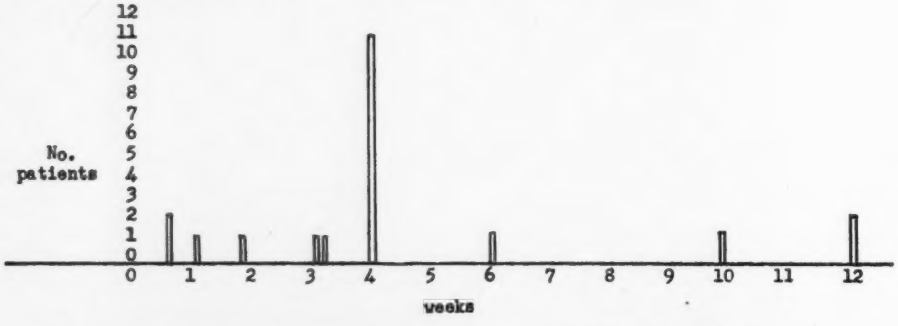


Fig. 6.—Chorionic gonadotrophin follow-up. Week at which test became negative.

Comment

Although the signs and symptoms of hydatidiform mole are well known, the correct diagnosis is infrequently made on admission. Since threatened abortion and hydatidiform mole are practically indistinguishable during the first trimester, one might suspect that the low percentage of correct diagnoses is due to a preponderance of cases at early gestational age. Actually, as was pointed out in our series and that of Cabrera,[3] the majority of cases are seen during the second trimester. Possible explanations for misdiagnosis are (1)

relative rarity of the disease, (2) a low index of suspicion on the part of the obstetrician, and (3) cursory examinations accorded the antenatal patient during the second trimester. The latter two conditions are certainly amenable to improvement.

In addition to the problem of diagnosis, the picture of hydatidiform mole is further complicated by the fact that 1 per cent of the moles develop into choriocarcinoma and about 15 per cent into malignant mole. This latter problem, as has been stressed already, is one of great magnitude and its successful resolution requires the keenest of judgment as well as all the diagnostic aids available.

Summary

1. A total of 38 cases of hydatidiform mole were encountered at the Pennsylvania Hospital during the past 22 years.

2. Two of 38 were of the malignant or invasive variety. There were no cases of chorionepithelioma.

3. The signs and symptoms of hydatidiform mole have been discussed, the problems of diagnosis emphasized, and the difficulties in follow-up stressed.

Appreciation is expressed to Drs. A. Reynolds Crane and J. Paul Decker, Department of Pathology, Pennsylvania Hospital, for their critical interpretation of the pathological material, and to Dr. S. Leon Israel, Obstetrician and Gynecologist, Pennsylvania Hospital, for his many helpful suggestions in the preparation of this manuscript.

References

1. Acosta-Sison, H.: Am. J. Obst. & Gynec. **53**: 133, 1947.
2. Brody, H., and Horowitz, E. A.: Am. J. Obst. & Gynec. **59**: 685, 1950.
3. Cabrera, S. H.: Bol. Soc. chilena de obst. y ginec. **11**: 39, 1946. (Abstract in Am. J. Obst. & Gynec. **55**: 1081, 1948.)
4. Cecil, A. B., and Krech, S.: Am. J. Obst. & Gynec. **68**: 930, 1954.
5. Eastman, N. J.: Williams Obstetrics, ed. 10, New York, 1950, Appleton-Century-Crofts, Inc., pp. 528-534.
6. Gaetane, J., and Labriola, B. F.: Am. J. Obst. & Gynec. **66**: 1331, 1953.
7. Gitman, L., Mitchell, N., and Dubin, A.: Am. J. Obst. & Gynec. **58**: 171, 1949.
8. Hennessy, J. P.: Am. J. Obst. & Gynec. **57**: 779, 1949.
9. Hertig, A. T., and Sheldon, W. H.: Am. J. Obst. & Gynec. **53**: 1, 1947.
10. Hunt, W., Dockerty, M. B., and Randall, L. M.: Obst. & Gynec. **1**: 593, 1953.
11. Jones, G. S.: The Management of Endocrine Disorders of Menstruation and Fertility, Springfield, Ill., 1954, Charles C Thomas, Publisher, pp. 140-155.
12. Kantor, A. E., and Mercer, T. H.: Am. J. Obst. & Gynec. **61**: 936, 1951.
13. Kuperstein, D., and Mackles, A.: Am. J. Obst. & Gynec. **68**: 1136, 1954.
14. Lull, C. B., and Kimbrough, R. A.: Clinical Obstetrics, Philadelphia, 1953, J. B. Lippincott Company, pp. 265-267, 422-425.
15. Moore, J. H.: Am. J. Obst. & Gynec. **69**: 205, 1955.
16. Mueller, C. W., and Lapp, W. A.: Am. J. Obst. & Gynec. **58**: 133, 1949.
17. Novak, E.: Am. J. Obst. & Gynec. **59**: 1355, 1950.
18. Novak, E.: Gynecologic and Obstetric Pathology, ed. 3, Philadelphia, 1952, W. B. Saunders Company, pp. 503-533.
19. Novak, E., and Seah, C. S.: Am. J. Obst. & Gynec. **67**: 933, 1954.
20. Novak, E., and Seah, C. S.: Am. J. Obst. & Gynec. **68**: 376, 1954.
21. Nuckols, H. H., and Fine, C. S.: Am. J. Obst. & Gynec. **65**: 990, 1953.
22. Pigeaud, H.: Gynéc. et obst. **48**: 470, 1949. (Abstract in Am. J. Obst. & Gynec. **63**: 1400, 1952.)
23. Savage, M. B.: Am. J. Obst. & Gynec. **62**: 346, 1951.
24. Stander, H. J.: Williams Obstetrics, ed. 7, New York, 1936, D. Appleton-Century Company, Inc., p. 710.
25. Velits, V., and Meyer, R.: Quoted by Hunt, Dockerty and Randall.[10]

THERAPEUTIC ABORTION AT THE CHICAGO LYING-IN HOSPITAL

MYRNA F. LOTH, M.D., AND H. CLOSE HESSELTINE, M.D., CHICAGO, ILL.

(From the Department of Obstetrics and Gynecology, The University of Chicago and the Chicago Lying-in Hospital)

THE subject of therapeutic abortion remains somewhat controversial. Originally, this procedure was advocated for the saving or prolongation of life of the patient, since it involved the termination of a presumably normal intrauterine gestation before the period of viability. Later, however, the indications have been extended to include conditions in which the physical or mental health of the patient would be seriously impaired by the continuation of the pregnancy. More recently severe and usually irremediable hereditary and congenital conditions of the fetus have been advanced as proper indications for therapeutic abortion. Social and economic factors have not been recognized legally or medically as valid considerations. This discussion will not delve into the legal aspects, but these requirements must be known and fulfilled by the physician before undertaking the procedure.

Review of Literature

There has been a rising interest in the problem of therapeutic abortion as evidenced by reports in the literature in recent years. Tietze[9] reported an unusually large series of 3,592 cases, with a ratio of 1:197.5 live births, an incidence very similar to that in this report. About 75 per cent of his cases were terminated by dilatation and curettage, in contrast with our incidence of only 28 per cent. A smaller series of 137 cases was reported by Moore and Randall,[3] with a ratio of 1:176 live births. These authors noted that there had been a decrease in the therapeutic abortion ratio at their hospital in recent years.

Shaefer and Epstein[6] discussed the problem with reference to pulmonary tuberculosis, and concluded that in most cases the end result after full-term delivery is better or at least no worse than after therapeutic abortion. Their series consisted of 63 abortions compared with 407 full-term deliveries, all in tuberculous patients. A stricter and more uniform control of therapeutic abortion and sterilization was advocated by Pearce and Ott,[4] who felt that permanent hospital committees should be set up to approve such procedures.

Stephenson[7] presented a series of 89 abortions with a ratio of 1:121 live births in a five-year period. He believes that many of the currently accepted indications are not valid and are in fact contrary to law. For example, in his opinion, no fetal indications should be allowable. Campbell,[1] on the other hand, favored a reconsideration of the indications for therapeutic abortion and sterilization in a more liberal direction, and felt that consideration of socio-

economic factors should be allowed because of their relationship to the patient's health and welfare. He, like Taussig,[8] suggested a complete revision of state laws pertaining to these procedures.

An excellent series of discussions of the medical, legal, psychiatric, and anthropological aspects of therapeutic abortion has been compiled and edited by Rosen.[5] In his book, special emphasis is placed on psychiatric indications, as well as on the psychic reaction of the patient following such a procedure.

Clinical Material

In a review of the series of therapeutic abortions performed at the Chicago Lying-in Hospital in the last quarter of a century, it is apparent that new concepts have arisen on the conditions which constitute proper indication for the termination of a pregnancy. In 1939, Hesseltine, Adair, and Boynton[2] presented an analysis of therapeutic abortions at this institution from May, 1931, to July, 1939. These data will serve as a basis of comparison for the present series, which covers the fifteen-year period from July 1, 1939, to July 1, 1954. During this latter period, a total of 301 pregnancies have been terminated for therapeutic purposes, in comparison with 57,635 deliveries at or near term over the same span of years. This gives a ratio of therapeutic abortions to deliveries of 1:191, or a percentage of 0.52. As can be noted in Table I, the ratio of the former period was 1:195 or 0.51 per cent. Thus the over-all ratio has remained unchanged.

TABLE I. INCIDENCE OF THERAPEUTIC ABORTION

	1931-1939	1939-1954	1931-1954
Number of therapeutic abortions	134	301	435
Number of deliveries	26,131	57,635	83,766
Ratio	1:195	1:191	1:193
Percentage	0.51	0.52	0.515

The yearly incidence has varied considerably during the period covered by this report, with a low of 7 cases in 1940 and a high of 29 cases in 1945 and 1946 (Table II). The average would be approximately 19 cases per year. Although the actual number of cases has been slightly higher than in the 1931-1939 series (which averaged about 17 cases per year), the number of deliveries increased proportionately during the latter period.

TABLE II. NUMBER OF THERAPEUTIC ABORTIONS PER YEAR (1939-1954)

YEAR	CASES
1939 (6 months)	3
1940	7
1941	10
1942	14
1943	27
1944	20
1945	29
1946	29
1947	24
1948	17
1949	22
1950	28
1951	16
1952	28
1953	19
1954 (6 months)	8

Procedures

In the majority of cases when therapeutic abortion is indicated, the patient's medical condition warrants the prevention of future gestations. In the present series, 209 patients (69.4 per cent) were sterilized, a slightly higher percentage than in the earlier group (67 per cent) (Table III).

TABLE III. INCIDENCE OF STERILIZATION PROCEDURE IN CONJUNCTION WITH THERAPEUTIC ABORTION

	1931-1939		1939-1954		1931-1954	
	NO.	%	NO.	%	NO.	%
Patient	90	67.0	209	69.4	299	68.7
Husband	3	2.0	1	0.4	4	0.9

Instances where sterilization may not be indicated would include such maternal disorders as severe hyperemesis gravidarum, certain cases of pulmonary tuberculosis, active rheumatic fever, rubella during the first trimester, and other conditions from which the patient may recover or improve medically to the extent that the present hazard would be likely not to recur. On the other hand, there are instances in which sterilization is indicated but is deferred as an unjustifiable surgical risk.

Very occasionally the question may be advanced as to the merit of sterilization of the husband instead of the patient. This is a personal matter and not one for the obstetrician to prescribe. The legal duties of the physician are confined to the patient and her treatment. If the husband raises the question, the patient's doctor can point out the simplicity of the procedure, but also its disadvantages in the event of remarriage of either of the partners. Only one husband is known to have undergone a sterilization procedure elsewhere during the period covered by the present series of cases.

The method of termination is influenced by such factors as the length of gestation, the age of the patient, the degree of surgical risk to the patient, and the advisability of concurrent sterilization. There has been a marked increase in recent years in the number of hysterectomies performed for this purpose, since hysterectomy affords the surest method of sterilization, and since modern medical advances have sharply decreased the risks of this procedure to the patient. An additional advantage of removal of the uterus and cervix is the elimination of existent or future disease of these organs. With the increase in hysterectomies has come a corresponding decrease in the number of abdominal hysterotomies and the associated tubal ligations. This is demonstrated in Table IV, which gives the incidences of the various methods of termination in the two series.

TABLE IV. METHODS OF TERMINATION

METHOD	1931-1939		1939-1954		1931-1954	
	NO. CASES	%	NO. CASES	%	NO. CASES	%
Hysterectomy	26	20.0	114	38.0	140	32.0
Hysterotomy and sterilization	67	50.0	89	30.0	156	36.0
Dilatation and curettage and sterilization	0	0.0	6	2.0	6	1.5
Dilatation and curettage	34	25.0	79	26.0	113	26.0
Hysterotomy	5	4.0	13	4.0	18	4.0
Bag induction	2	1.0	0	0.0	2	0.5
Total	134	100.0	301	100.0	435	100.0

Indications for Therapeutic Abortion

The primary indications for therapeutic abortion are found in two main groups: first, cardiac disease, and second, diseases of the renovascular system. There has been a rather sharp decline in the number of pregnancies terminated because of pulmonary disease and especially for pulmonary tuberculosis. In recent years a new category among the indications, the abnormal fetal conditions, has shown increased prominence. The term "fetal indication" is used for brevity and convenience; actually it is only partially fetal because in most of these cases the pregnancy is terminated because of emotional stress in the mother, as well as the prevention of serious or irremediable hereditary or congenital defects in the fetus.

A summary of the general classification of indications in this survey is shown in Table V.

TABLE V. INDICATIONS FOR THERAPEUTIC ABORTION

INDICATION	1931-1939		1939-1954		1931-1954	
	NO. CASES	%	NO. CASES	%	NO. CASES	%
Cardiac	27	20.0	77	26.0	104	24.0
Renovascular	34	25.5	77	26.0	111	26.0
Psychiatric and neurological	20	15.0	46	15.0	66	15.0
Pulmonary	30	22.5	40	13.0	70	16.0
Maternal-fetal	0	0.0	22	7.0	22	5.0
Miscellaneous	23	17.0	39	13.0	62	14.0
Total	134	100.0	301	100.0	435	100.0

With the advent of greater obstetrical knowledge and more modern medical techniques, maternal mortality from infection and hemorrhage has decreased to such a low number that cardiac, hypertensive, and renovascular diseases have become more prominent in the etiology of obstetrical deaths. Among the cardiac lesions, rheumatic heart disease is by far the most common. The obstetrician and cardiologist together must evaluate fully the risks involved in the continuation of the pregnancy as against the insult of termination of the gestation. The cardiac indications in the present series fall into five categories (Table VI).

TABLE VI. CARDIAC INDICATIONS

	NO.	%
1. Rheumatic heart disease	67	87.0
2. Congenital heart disease	5	6.5
3. Coarctation of aorta	2	2.5
4. Myocardial degeneration	2	2.5
5. Adhesive pericarditis	1	1.5
Total	77	100.0

TABLE VII. RENOVASCULAR INDICATIONS

	NO.	%
1. Hypertension and hypertensive cardiovascular disease	42	54.5
2. Glomerulonephritis	15	20.0
3. Toxemia	13	17.0
4. Nephrolithiasis	4	5.0
5. Pyelonephritis	2	2.5
6. Polycystic kidneys	1	1.0
Total	77	100.0

The classification of the renovascular group includes the toxemias (hypertensive and pre-eclamptic), essential hypertension, nephritis, and other renal diseases. These are described in Table VII.

Psychiatric indications have become a most controversial matter. Some authors have stated arbitrarily that therapeutic abortion should never be performed for this reason, while others have felt as strongly that mental disease is as valid an indication as other medical ones. There has been no particular change in attitude at the Chicago Lying-in Hospital, for the two periods studied. Over the years the attitude has been one of caution. Views on neurological conditions which would be dangerous complications have been more stable. The distribution of the neurological and psychiatric indications is indicated in Table VIII.

TABLE VIII. PSYCHIATRIC AND NEUROLOGICAL INDICATIONS

	NO.	%
1. Psychoneurosis	17	37.0
2. Psychosis	4	9.0
3. Psychopathic personality	2	4.5
4. Idiocy	3	6.5
5. Epilepsy	8	17.5
6. Multiple sclerosis	3	6.5
7. Poliomyelitis	4	9.0
8. Friedreich's ataxia	1	2.0
9. Sydenham's chorea	1	2.0
10. Cerebral agenesis	1	2.0
11. Guillain-Barré syndrome	1	2.0
12. Paraplegia	1	2.0
Total	46	100.0

There has been a notable reduction in the number of pregnancies interrupted because of pulmonary tuberculosis, primarily due to improved medical therapy of the disease. The incidence has decreased from 22.5 to 13 per cent. All of the pulmonary indications constitute only about 15 per cent of the total group (Table IX).

TABLE IX. PULMONARY INDICATIONS

	NO.	%
1. Pulmonary tuberculosis	34	85.0
2. Bronchiectasis	3	7.5
3. Pulmonary fibrosis	1	2.5
4. Pulmonary cystic disease	1	2.5
5. Asthmatic bronchitis	1	2.5
Total	40	100.0

Fetal indications were accepted in the instances where the product of gestation was certainly defective, and also where severe emotional factors in the mother were clearly established. From this latter aspect, one might have included these under psychiatric indications; however, there were special issues related to the fetus. This applied in the cases of Rh incompatibility and especially where the mother had repeatedly suffered the loss of infants at birth due to erythroblastosis.

Attitudes have become less certain on the likelihood of fetal injury from maternal rubella in the first trimester. The trend in recent years has been less toward termination of the pregnancy. It appears that these infections in the United States have not been as damaging to the fetus as was reported from Australia. The individual maternal-fetal indications have been catalogued under 8 headings (Table X).

TABLE X. FETAL INDICATIONS

	NO.	%
1. Rubella in the first trimester	8	36.0
2. Rh incompatibility	8	36.0
3. Amaurotic familial idiocy in previous children	1	5.0
4. Mongolism in previous children	1	5.0
5. Gargoylism in previous children	1	5.0
6. Epilepsy in previous children	1	5.0
7. Familial diabetes	1	5.0
8. Little's disease in previous children	1	5.0
Total	22	100.0

There remained 39 other cases which fell into 16 categories. These were placed in a miscellaneous group for convenience of presentation. With the advance of medical science, some of these have become less often needed. Hyperemesis gravidarum, for example, seldom reached the intractable stage. The position has been taken that, with firm and intensive early therapy, it would cease to be an indication. Leiomyomas of the uterus should not be an indication for removal of the fetus but in exceptional situations degenerative or hemorrhagic changes, hemorrhage, or incompatible size has dictated the removal of the uterus and leiomyomas with the pregnancy. The product of conception was removed because there was no alternate choice. The termination of pregnancy without treatment of the myomas would be inconsistent and improper treatment. Diabetes mellitus has not occurred as an indication since 1949. It should be a rare instance in which the diabetic pregnant patient could not be carried to the time of fetal viability if not to term by adequate medical management. Pregnancy has had such an unfavorable influence upon malignancies in general that drastic measures have often been indicated. Other miscellaneous indications and their incidence have been tabulated (Table XI).

TABLE XI. MISCELLANEOUS INDICATIONS

	NO.	%
1. Leiomyomas of the uterus	7	18.0
2. Diabetes mellitus	5	13.0
3. Hyperemesis gravidarum	4	10.0
4. Carcinoma	4	10.0
5. Colitis	3	8.0
6. Arthritis	3	8.0
7. Lupus erythematosus	2	5.0
8. Progressive otosclerosis	2	5.0
9. Hyperthyroidism	2	5.0
10. Lymphosarcoma	1	2.5
11. Diabetes insipidus	1	2.5
12. Thrombophlebitis	1	2.5
13. Recurrent rectovaginal fistula	1	2.5
14. Severe intractable anemia	1	2.5
15. Brucellosis with central nervous system involvement	1	2.5
16. Amebiasis with hepatitis	1	2.5
Total	39	100.0

Discussion of Results

The merits of any procedure must be evaluated according to the end results (Table XII). Fifty-five patients did not return or were not followed satisfactorily. They represented 18 per cent of the series. The favorable results (64 per cent good and 5 per cent fair) equaled 69 per cent, the poor

and unchanged group totaled 12.6 per cent. If the undetermined group was a true cross section then the satisfactory percentage would be approximately 85 per cent while the unsatisfactory segment would amount to approximately 15 per cent. There is, however, no assurance that the undetermined number would be so distributed.

TABLE XII. EVALUATION OF RESULTS

RESULT	NUMBER	%
Good	193	64.1
Fair	15	5.0
Poor	13	4.3
Unchanged	25	8.3
Undetermined	55	18.3
Total	301	100.0

In retrospect there has been an occasional instance in which the indication seemed inadequate, or the method of termination not satisfactory. Nevertheless, each patient was carefully evaluated, and when all factors were considered the decision was agreed upon by the patient's physician and the consultants.

Even with the exercise of the best safeguards a few complications were incidental to the procedure. These included: (a) perforation of the uterus in three cases at the time of dilatation and curettement (these were on teaching services), (b) dehiscence of the abdominal incision twice, (c) moderately severe postoperative infections three times, and (d) incomplete evacuation of the uterus twice.

In the entire series there was no immediate postoperative mortality, and of the patients who were followed over a period of time, only three are known to have died, one of malignant hypertension five months after operation, and two of chronic glomerulonephritis four months and three years, respectively, after therapeutic abortion. The evaluation of results fell rather definitely into one of five categories: good, fair, poor, unchanged, and undetermined. Only 4.3 per cent were considered unsatisfactory or poor.

Summary

A statistical analysis has been made of 301 therapeutic abortions performed at the Chicago Lying-in Hospital over a fifteen-year period. These data were compared with similar data from the preceding eight years. The total time is from the opening of the present Chicago Lying-in Hospital on May 25, 1931, up to June 30, 1954.

Comments on the indications and technical methods have been given. An attempt has been made to designate changes in the indications as well as in the procedures. In 69 per cent of the cases the results have been adjudged satisfactory. Only 12.6 per cent of the group had an unsatisfactory outcome. The remaining percentage of patients did not return. Thus the procedures

were properly chosen, for by critical appraisal the outstandingly favorable results speak for themselves. It is obvious that the future will witness changes in indications and management as medical science advances.

References

1. Campbell, J. V.: West. J. Surg. 58: 371, 1950.
2. Hesseltine, H. C., Adair, F. L., and Boynton, M. W.: AM. J. OBST. & GYNEC. 39: 549, 1940.
3. Moore, J. G., and Randall, J. H.: AM. J. OBST. & GYNEC. 63: 28, 1952.
4. Pearce, H. A., and Ott, H. A.: AM. J. OBST. & GYNEC. 60: 285, 1950.
5. Rosen, H.: Therapeutic Abortion, New York, 1954, Julian Press, Inc.
6. Schaefer, G., and Epstein, H.: AM. J. OBST. & GYNEC. 63: 129, 1952.
7. Stephenson, H. A.: Obst. & Gynec. 4: 578, 1954.
8. Taussig, F. J.: Abortion, Spontaneous and Induced, St. Louis, 1936, The C. V. Mosby Company.
9. Tietze, C.: AM. J. OBST. & GYNEC. 60: 146, 1950.

PRETERM DELIVERY OF ERYTHROBLASTOTIC INFANTS

TOMMY N. EVANS, M.D., ANN ARBOR, MICH.

(From the Department of Obstetrics and Gynecology, University of Michigan)

AS YET there is no known method of preventing maternal Rh sensitization or its damaging effects on the fetus. Although this objective has not been attained, earlier recognition of erythroblastosis and improved pediatric treatment have increased fetal salvage. More extensive adaptation of current diagnostic and therapeutic methods will increase further the survival rate for erythroblastotic infants.

Despite this improvement, the problem of intrauterine fetal death from erythroblastosis continues to be regarded with pessimism. Within a few years after recognition of the pathogenesis of erythroblastosis, *premature* delivery of erythroblastotic infants was widely practiced. Subsequent interpretation of the results from this approach suggested that the addition of prematurity to erythroblastosis decreased the chances for fetal survival. As a consequence *premature* interference with these pregnancies was abandoned. This change in attitude toward interruption of pregnancy, however, was based on experience with such management when the importance of the degree of fetal maturity and the benefits of current treatment of the infant were not fully appreciated. Because of the many instances of stillbirth of erythroblastotic infants and because of improved methods of treating erythroblastosis, re-evaluation of early delivery of these infants seemed desirable. This report covers our results following utilization of *preterm,* not *premature,* delivery as part of the therapeutic program.

Treatment of Newborn Infants in Presence of Rh Incompatibility.—Facilities for diagnosis of erythroblastosis and institution of optimum treatment during the first few hours of life are of major importance. As an emergency procedure immediately after birth, the Coombs test[1] with positive and negative controls is done on the cord blood of every infant with an Rh-negative mother. This will identify all infants with erythroblastosis except those in cases where the mother is Rh positive and the disease is due to the major group factors or the small "c" factor (Table I, Cases 8 and 9). Because of the latter possibility, careful attention should be directed toward any baby who develops jaundice, particularly during the first 24 to 36 hours of life. Until the Coombs test is reported as negative (within one hour), a 4 or 5 inch segment of umbilical cord is left attached to a baby of an Rh-negative mother. This technically facilitates the performance of an exchange transfusion should it be necessary, i.e., when the Coombs test is positive and there is anemia or rapidly developing jaundice. When the Coombs test is positive with no anemia at birth, serial hemoglobin determinations must be done along with close observation of the infant. Usually, for the transfusion, 500 c.c. of group specific, Rh-negative

blood is used when the infant is Rh positive. When this is not available, or in an emergency, group O, Rh-negative blood with the addition of Whitebsky substances is used. Fresh blood is preferred—at most two or three days old.[2]

Anticipation of Erythroblastosis.—With the availability of the Coombs test and facilities for performance of an exchange transfusion at any hour, less and less importance has been attached to antepartum maternal Rh antibody determinations. When such facilities are not constantly available, however, and preparations for the care of each erythroblastotic infant must be made individually, antepartum identification of the sensitized mother assumes greater importance.

Presence of Rh antibodies in maternal blood proves only that sensitization has occurred as a result of a previous Rh-positive baby or blood transfusion. It does not prove the presence of an Rh-positive fetus or the severity of erythroblastosis. A rising Rh antibody titer has been observed with a normal Rh-negative fetus after the mother had been sensitized by a previous Rh-positive baby.[3] Also, low and at times undetectable levels of maternal Rh antibodies have been associated with severely affected erythroblastotic infants. Although a rising maternal Rh antibody titer in the last trimester generally increases the likelihood of the presence of an erythroblastotic fetus, because of the discrepancies mentioned, the titer of maternal Rh antibodies no longer influence our management of the pregnancy or treatment of the infant.

Presence of maternal Rh antibodies, in any amount, or a positive indirect Coombs test on maternal blood in any dilution is significant in confirming maternal sensitization and increases the possibility of a subsequent erythroblastotic infant. Once it has been established that a mother is sensitized, repetition of such testing with a subsequent pregnancy seems superfluous.

The past obstetric history is still the most reliable criterion in anticipating an erythroblastotic infant. After a mother has had an erythroblastotic infant, if her husband is homozygous Rh positive, virtually all subsequent infants will have erythroblastosis. As a rule the first erythroblastotic infant is only mildly affected and survives with proper treatment. Subsequent erythroblastotic infants are generally progressively more seriously affected. If the husband is heterozygous Rh positive, there is a 50 per cent chance that subsequent pregnancies will produce an unaffected Rh-negative infant.[4] Although laboratory determination of the husband's zygosity involves a small potential error, thus far in our experience it has proved to be correct except in one instance (Table I, Case 4).

Preterm Interruption of Pregnancy.—Because of the high perinatal mortality rate from erythroblastosis in the past, *preterm,* but *not premature,* termination of pregnancy has been carried out during the past four years in mothers who have had previous erythroblastotic stillborn infants or babies with severe disease at birth. When the history of amenorrhea and the clinical and x-ray findings indicated that the pregnancy was of at least 8 months' duration and that prematurity would no longer play a major role in fetal survival, these pregnancies were terminated by medical and/or surgical induction of labor. Of the 11 cesarean sections in the preterm delivery group, 7 were carried out after repeated failures to induce labor and 3 because of previous cesarean sections. Because of a general tendency toward recurrence of intrauterine deaths from erythroblastosis during the same period of gestation, the time of previous fetal deaths also was considered in the selection of time for interruption of pregnancy.

Since institution of this program, *preterm* delivery was carried out in 26 pregnancies involving 27 infants.

TABLE I. PRETERM DELIVERY OF WOMEN WITH HOMOZYGOUS RH-POSITIVE HUSBANDS AFTER PREVIOUS STILLBIRTHS OF ERYTHROBLASTOTIC INFANTS

CASE	PARITY	PREVIOUS ERYTHROBLASTS	PREVIOUS STILLBIRTHS	PREVIOUS NEONATAL DEATHS	HUSBAND'S GENOTYPE ZYGOSITY	WEEKS OF PREGNANCY	ARTIFICIAL INDUCTION OF LABOR	CESAREAN SECTION	INFANT'S WEIGHT (GRAMS)	COOMBS TEST	HGB. (GM. %)	RBC (MILLION PER C. M.M.)	EXCHANGE TRANSFUSION	END RESULT (AGE)
1. S. B.	v	4	4	0	CDe/CDe Homo-	36	0	X	1,956	+	7.8	2.6	X	Normal infant (4 years)
2. R. K.	ii	1	1	0	CDe/cDE Homo-	37	X	0	3,459	+	9.5	3.0	X	Normal infant (2¼ years)
3. I. F.	v	2	2	0	CDE/CDe Homo-	35	0	X	2,620	+	6.0	1.5	X	Normal infant (1½ years)
4. S. B.	vi	5	4	0	CDe/CDe Homo-	37	0	X	2,485	–			0	Rh-negative infant
5. M. E.	ii	1	1 (? cause)	0	CDe/cDE Homo-	39	0	X	2,565	+	8.0	2.0	X	Neonatal death
6. R. D.	iv	2	1	1	CDe/cDE Homo-	37	0	X	2,460	+	14.5	--	X	Neonatal death
7. E. L.	iii	2	1	1	CDe/cDE Homo-	36	0	X	2,721	+	8.5	--	X	Normal infant (6 weeks)

Data on Series of Preterm Deliveries

Preterm Delivery After Previous Stillbirths of Erythroblastotic Infants.—The first 7 cases (Table I) represent patients who have had from one to four previous stillbirths, and whose husbands from the probable genotype were thought to be homozygous Rh positive. Except for Case 4, which represents an additional pregnancy of the first patient, all of the infants had severe erythroblastosis, as was evidenced by the positive Coombs test, the low hemoglobin, and the infants' Rh status, as well as by the subsequent clinical course. The infants in Cases 5 and 6 died on the second and third days of life. Although the other changes characteristic of erythroblastosis were found at the time of autopsy. there was no evidence of kernicterus. In addition to extensive hepatic necrosis, there also was pulmonary hyaline membrane in Case 6. This last case conforms to the observations of others that often there is a poor correlation between the degree of anemia at birth and the severity of the disease. Much to our surprise, following four previous stillbirths of erythroblastotic infants and a subsequent satisfactory outcome of a preterm delivery by cesarean section with prompt exchange transfusion in Case 1, this patient was delivered subsequently of an Rh-negative infant (Case 4). This is the only example in our experience wherein the zygosity of the husband's blood, as determined in the laboratory, did not conform with the blood of subsequent infants.

Cases 8 and 9 (Table II) represent two separate pregnancies of the same patient wherein an Hr incompatibility existed. This patient's first delivery involved a stillborn infant delivered elsewhere. Although autopsy was performed, the cause of death was not evident. The second infant died neonatally as a result of erythroblastosis. During the third pregnancy artificial induction of labor was carried out after 36 weeks with delivery of an erythroblastotic infant who survived after exchange transfusion and is now normal. Approximately one and one-half years later a repeat performance was carried out by the patient with a similarly satisfactory outcome following the same treatment. Both of these infants appear to be entirely normal. The tenth and eleventh cases (Table III) also involve the same patient who had a previous stillbirth and a total of two previous erythroblastotic infants by a heterozygous Rh-positive husband. During the thirty-sixth week of pregnancy and prior to our planned artificial interruption of this pregnancy because the infant was so small, the patient went into labor spontaneously and delivered a 1,531 gram infant with 5.5 Gm. per cent of hemoglobin and only 1.1 million red blood cells. The Combs test was positive and an exchange transfusion was carried out, resulting in a normal infant. It is probable that the spontaneous intervention of labor in this patient was responsible for the survival of the infant. A second pregnancy of this patient was again terminated by premature spontaneous labor with delivery of a 2,250 gram normal infant that was Rh negative. This conforms with the previously determined heterozygosity of the husband. A third patient in this group (Table III, Case 12) had had a previous stillborn infant by a heterozygous husband. Following artificial induction of labor after 37 weeks of pregnancy, an Rh-negative infant was delivered.

Fetal Salvage After Neonatal Deaths of Previous Erythroblastotic Infants.—The next 4 pregnancies (Table IV, Cases 13-16) involved patients who did not present a history of previous stillbirths but rather one of early neonatal deaths from erythroblastosis. In all 4 instances, the husband was homozygous Rh positive. In 2 cases, artificial induction of labor was carried out after 37 weeks of pregnancy with delivery of erythroblastotic infants who received immediate exchange transfusions and are now normal. The other 2 patients were delivered

TABLE II. PRETERM DELIVERY AFTER PREVIOUS NEONATAL DEATHS OF ERYTHROBLASTOTIC INFANTS FROM Hr INCOMPATIBILITY

CASE	PARITY	PREVIOUS ERYTHROBLASTS	PREVIOUS STILLBIRTHS	PREVIOUS NEONATAL DEATHS	HUSBAND'S GENOTYPE, ZYGOSITY	WEEKS OF PREGNANCY	ARTIFICIAL INDUCTION OF LABOR	CESAREAN SECTION	INFANT'S WEIGHT (GRAMS)	COOMBS TEST	HGB. (GM. %)	RBC (MILLION PER C. MM.)	EXCHANGE TRANSFUSION	END RESULT (AGE)
8. B. R.	ii	1	1 (? cause)	1	Hr Incompatible	36	X	0	2,410	+	11.8	3.0	X	Normal infant (2¼ years)
9. B. R.	iii	2	1 (? cause)	1	Hr Incompatible	37	X	0	2,835	+	12.0	3.4	X	Normal infant (1 year)

TABLE III. PRETERM DELIVERY OF WOMEN WITH HETEROZYGOUS Rh-POSITIVE HUSBANDS AFTER PREVIOUS STILLBIRTHS OF ERYTHROBLASTOTIC INFANTS

CASE	PARITY	PREVIOUS ERYTHROBLASTS	PREVIOUS STILLBIRTHS	PREVIOUS NEONATAL DEATHS	HUSBAND'S GENOTYPE, ZYGOSITY	WEEKS OF PREGNANCY	ARTIFICIAL INDUCTION OF LABOR	CESAREAN SECTION	INFANT'S WEIGHT (GRAMS)	COOMBS TEST	HGB. (GM. %)	RBC (MILLION PER C. MM.)	EXCHANGE TRANSFUSION	END RESULT (AGE)
10. E. A.	iii	2	1	0	CDe/cde Hetero-	36	0	0	1,531	+	5.5	1.1	X	Normal infant (3¼ years)
11. E. A.	iv	3	1	0	CDe/cde Hetero-	35	0	0	2,250	–	24.0	6.7	0	Rh-negative infant
12. P. S.	iv	2	1	0	cDE/cde Hetero-	37	X	0	2,620	–	18.0	6.0	0	Rh-negative infant

TABLE IV. PRETERM DELIVERY OF PATIENTS WITH HOMOZYGOUS RH-POSITIVE HUSBANDS AFTER PREVIOUS NEONATAL DEATHS OF ERYTHROBLASTOTIC INFANTS

CASE	PARITY	PREVIOUS ERYTHROBLASTS	PREVIOUS STILLBIRTHS	PREVIOUS NEONATAL DEATHS	HUSBAND'S GENOTYPE, ZYGOSITY	WEEKS OF PREGNANCY	ARTIFICIAL INDUCTION OF LABOR	CESAREAN SECTION	INFANT'S WEIGHT (GRAMS)	COOMBS TEST	HGB. (GM. %)	RBC (MILLION PER C. MM.)	EXCHANGE TRANSFUSION	END RESULT (AGE)
13. M. A.	ii	1	0	1	CDe/cDE Homo-	37	X	0	2,892	+	11.7	3.2	X	Normal infant (2¾ years)
14. M. S.	iv	2	0	1	CDe/CDe Homo-	38	0	X	3,090	+	10.0	3.8	X	Normal infant (2½ years)
15. M. S.	v	3	0	1	CDe/CDe Homo-	37	0	X	3,345	+	11.0	4.0	X	Normal infant (1½ years)
16. R. W.	iv	2	0	2	CDe/CDe Homo-	37	X	0	2,800	+	7.0	1.8	X	Normal infant (1½ years)

TABLE V. PRETERM DELIVERY AFTER PREVIOUS ERYTHROBLASTOTIC NEONATAL DEATHS WITH HETEROZYGOUS RH-POSITIVE HUSBANDS

CASE	PARITY	PREVIOUS ERYTHROBLASTS	PREVIOUS STILLBIRTHS	PREVIOUS NEONATAL DEATHS	HUSBAND'S GENOTYPE, ZYGOSITY	WEEKS OF PREGNANCY	ARTIFICIAL INDUCTION OF LABOR	CESAREAN SECTION	INFANT'S WEIGHT (GRAMS)	COOMBS TEST	HGB. (GM. %)	RBC (MILLION PER C. MM.)	EXCHANGE TRANSFUSION	END RESULT (AGE)
17. E. G.	ii	1	0	1	cDE/cde Hetero-	37	X	0	2,807	+	14.0	3.9	X	Normal infant (2¼ years)
18. H. S.	iv	2	0	1	cDE/cde Hetero-	38	X	0	3 034	+	13 0	4.2	X	Normal infant (2 years)
19. H. S.	v	3	0	1	cDE/cde Hetero-	38	X	0	3,770	+	8.5	4.8	X	Normal infant (6 months)

after 37 and 38 weeks, respectively, by cesarean section after failure of artificial induction of labor on two occasions. Both of these infants were also erythroblastotic and are now normal following exchange transfusions.

The next 3 pregnancies (Table V, Cases 17, 18, and 19) involved patients who had previous early neonatal deaths from erythroblastosis but whose husbands were heterozygous Rh positive. In all 3 instances, *preterm* induction of labor was carried out yielding erythroblastotic infants who are now normal.

Preterm Delivery After Survival of Previous Infants.—The next 7 cases (Table VI, Cases 20-26) represent patients who had previous infants severely erythroblastotic at birth but who had no previous perinatal deaths. One of the previous infants has nerve deafness and another is mentally defective. Five of these patients had homozygous, 2 heterozygous Rh-positive husbands. In 4 instances, artificial induction of labor was carried out, and in Cases 22 and 23 cesarean section was done following failure of attempts to induce labor artificially. After the onset of premature labor, Patient K. M., Case 24, was delivered by cesarean section because of a previous cesarean section for toxemia. In every instance, except for the development of retrolental fibroplasia in Case 20, the patient had an erythroblastotic infant that was entirely normal following exchange transfusion. One of the twins of Case 24 was Rh negative and, therefore, unaffected. Incidentally, the infant with retrolental fibroplasia shows no residual stigma from erythroblastosis.

Erythroblastosis and Prematurity.—Deliberate *premature* delivery was carried out in only one patient (Table VII, Case 27) who had three previous erythroblastotic stillborn infants prior to the last month of pregnancy. Because of this patient's consistency in so far as repeated intrauterine deaths were concerned and because her husband is homozygous Rh positive, cesarean section was carried out at the end of 33 weeks of pregnancy. This was done with the realization that an erythroblastotic infant with that degree of prematurity had a very poor prognosis. The infant was edematous at birth, with a slightly protuberant abdomen, and weighed 2,608 grams. The Coombs test was positive and the hemoglobin was 8.0 Gm. Despite immediate exchange transfusion, the baby died on the third day and autopsy showed kernicterus.

Other Erythroblastotic Infants.—The preceding cases do not represent all erythroblastotic infants delivered during this period. There were 8 affected infants without erythroblastotic siblings (Table VIII). Since routine examination of maternal blood for Rh antibodies had been abandoned, none of these 8 erythroblastotic infants was anticipated prenatally. The diagnosis was promptly established, however, by the routine performance of the Combs test on cord blood when the mother was Rh negative. Four received exchange transfusions, 2 with lesser degrees of anemia received small transfusions, and 2 required no treatment. All 8 now appear normal. In the 4 instances where exchange transfusion was required, *preterm* induction of labor would be advocated with subsequent pregnancies.

There were 4 pregnancies (one set of twins) wherein fetal death from erythroblastosis occurred before the last month of pregnancy (Table VIII). One of these patients was previously discussed (Case 21). During the recent subsequent pregnancy, however, hydramnios began during the sixth month and a hydropic infant was delivered during the thirty-third week. In pregnancies suspected of involving an erythroblastotic fetus, hydramnios is a grave prognostic sign. The preceding case was the only one where early fetal death occurred after a previous favorable outcome with preterm delivery. There were 5 other patients who had two consecutive preterm interruptions with uniformly good results (Case 1 and 4, 8 and 9, 10 and 11, 14 and 15, 18 and 19).

TABLE VI. PRETERM DELIVERY OF ERYTHROBLASTOTIC INFANTS WITHOUT PREVIOUS PERINATAL DEATHS

CASE	PARITY	PREVIOUS ERYTHROBLASTS	PREVIOUS STILLBIRTHS	PREVIOUS NEONATAL DEATHS	HUSBAND'S GENOTYPE, ZYGOSITY	WEEKS OF PREGNANCY	ARTIFICIAL INDUCTION OF LABOR	CESAREAN SECTION	INFANT'S WEIGHT (GRAMS)	COOMBS TEST	HGB. (GM. %)	RBC (MILLION PER C. MM.)	EXCHANGE TRANSFUSION	END RESULT (AGE)
20. K. P.	ii	1	0	0	CDe/CDe Homo-	37	X	0	2,807	+	10.3	3.7	X	Retrolental fibroplasia (3¼ years)
21. G. H.	ii	1	0	0	CDe/CDe Homo-	37	X	0	2,750	+	11.0	3.8	X	Normal infant (2¾ years)
22. M. L.	ii	1	0	0	CDe/CDe Homo-	38	0	X	3,110	+	7.5	1.9	X	Normal infant (1½ years)
23. V. H.	viii	3	0	0	CDe/CDe Homo-	38	0	X	2,900	+	12.0	4.0	X	Normal infant (1¼ years)
24. K. M.	i	0	0	0	CDE/cde Hetero-	37	0	X	a. 2,500	a. +	a. 13.7	a. 3.5	a. X	a. Normal (1 year)
								(Repeat)	b. 2,400	b. –	b. 21.0	b. 6.7	b. --	b. Rh-negative infant
25. H. W.	i	1	0	0	CDE/cDE Homo-	38	X	0	3,140	+	12.0	3.8	X	Normal infant (1 year)
26. E. M.	v	1	0	0	CDe/cde Hetero-	38	X	0	3,742	+	16.0	4.2	X	Normal infant (3 months)

TABLE VII. PREMATURE DELIVERY AFTER THREE PREVIOUS EARLY ERYTHROBLASTOTIC FETAL DEATHS

CASE	PARITY	PREVIOUS ERYTHROBLASTS	PREVIOUS STILLBIRTHS	PREVIOUS NEONATAL DEATHS	HUSBAND'S GENOTYPE, ZYGOSITY	WEEKS OF PREGNANCY	ARTIFICIAL INDUCTION OF LABOR	CESAREAN SECTION	INFANT'S WEIGHT (GRAMS)	COOMBS TEST	HGB. (GM. %)	RBC (MILLION PER C. MM.)	EXCHANGE TRANSFUSION	END RESULT
27. M. T.	iv	3	3	0	CDe/cDE Homo-	33	0	X	2,608	+	8.0	2.0	X	Neonatal death

TABLE VIII. OTHER ERYTHROBLASTOTIC INFANTS DELIVERED DURING SAME PERIOD (1951-1955)

I. First erythroblastotic		8
a. Exchange transfusions	4	
b. Small transfusions	2	
c. No treatment	2	
II. Fetal deaths before last month of pregnancy		5

Comment and Summary

Since the adoption of *preterm* delivery, when prematurity should not be a factor in fetal survival, and the use of prompt exchange transfusion, salvage of erythroblastotic infants has been definitely improved. The 26 patients treated in this manner had a 36.7 per cent survival rate among their previous erythroblastotic infants. This is a particularly poor salvage since in 11 cases there had been no more than one previous erythroblastotic infant and the first one is generally mildly affected. With *preterm* delivery and exchange transfusion, these same patients had a fetal survival of 91 per cent. Although one of the survivors has retrolental fibroplasia, none has any residual stigma from erythroblastosis. Four-Rh-negative infants were delivered before term. One of these had an erythroblastotic twin.

It is probable that some of these infants would have survived without preterm delivery. But it seems just as probable that many would not have survived without such intervention. Furthermore, the anathema associated in the past with delivery of such infants before term seems clearly unjustified. In retrospect, the poor results in the past were probably due as much to delayed and inadequate pediatric treatment as to premature delivery. Nevertheless, a sick infant who is definitely premature has less chance for survival than if he were mature. The one instance of delivery before the last month (Table VII, Case 27) offers no encouragement since the infant died and had kernicterus. Yet this is but one case, and such a practice seems justified when there have been repeated early fetal deaths and the husband is homozygous Rh positive. Fortunately such cases are in the minority.

Despite the extent of the discussion relating to the delivery of these infants, the fact that the prompt and excellent treatment administered by our Department of Pediatrics played the principal role in their survival is given due emphasis. Each erythroblastotic infant received only one exchange transfusion, although one (Table VI, Case 26) was given a small additional transfusion one month later. Often, time is of the essence. Delay in diagnosis and exchange transfusion, when indicated, will result in preventable infant deaths. In order that salvage may remain at a high level, the Coombs test should be run routinely on the cord blood of every infant with an Rh-negative mother, and every instance of jaundice during the first 24 to 36 hours of life must be intensively investigated. When the infant is affected at birth, prompt exchange transfusion must be regarded as the best treatment available at the present and must be carried out as an emergency procedure.

Although the salvage rate has been decidedly improved, such a therapeutic approach has nothing to offer when fetal death occurs early in pregnancy (Table VIII). There remains a critical need for some method of preventing isoimmunization or its damaging fetal effects.

References

1. Coombs, R. R. A., Mourant, A. E., and Race, R. R.: Lancet 1: 264, 1946.
2. Heyn, Ruth: Personal communication, 1955.
3. Evans, T. N.: Obst. & Gynec. 3: 80, 1946.
4. Pickles, M. M.: Haemolytic Disease of the Newborn, Springfield, Ill., 1949, Charles C Thomas, Publisher.

REPOSITORY CURARE IN NORMAL OBSTETRICS, A CONTROLLED STUDY*

ELLIS N. COHEN, M.D., HUBERT H. THEISSEN, M.D., AND JOSEPH MARVIN, M.D.,
ST. PAUL, MINN.

(From the Departments of Anesthesiology and Obstetrics, Charles T. Miller Hospital)

CURARE in repository forms has proved a useful adjunct in the relief of muscle spasm in a variety of painful conditions. Many reports of its successful use in orthopedics,[1] anorectal surgery,[2, 3] traumatic conditions, [4, 5] etc., are to be found in the current literature.

Laborit and collaborators[6] in 1948 reported on the "analgesia and acceleration of labor by a curare-spasmalgine combination." These authors used an aqueous suspension of tubocurarine given intramuscularly and repeated every 2 to 3 hours. Following this report other investigators in this country, Katzman and co-workers,[7] Hartnett and Freiheit,[8] McMann,[9] and Jewell,[10] utilized aqueous curare compounds in small and larger series of routine obstetrical patients. These various workers reported analgesic effects, acceleration of labor, shallower episiotomies, and a facilitation of forceps application and delivery.

With the availability of a satisfactory form of repository curare,† producing on single injection a sustained blood level of curare for 8 to 12 hours,[11] it was thought worth while to study the effects of this preparation on the obstetrical patient. Since the personal factor necessarily enters into such measurements as pain relief, muscle relaxation, etc., it was felt that the significance of this study would be completely dependent upon careful controls. Accordingly, 200 consecutive normal obstetrical patients were alternately given an injection of repository curare (Lenahan's[2] schedule), or an identical placebo without the active curare principle. Injections were given at the beginning of active labor or the achievement of dilatation of 3 to 4 cm. Only code numbers were available to those participating in the study, and the code numbers were changed at intervals. Only in the final tabulation of the data sheets was the control group separated from the drug series. All patients were given routine obstetrical care according to the practice of the attending physician.

The results of the study are summarized in Tables I to V.

These tables plus the data sheets were subjected to careful statistical study. The results of this survey point out once again the value of controlled study and an analysis by statistical techniques. Except in Table I no sig-

*This study was supported through a grant from the Lewis and Annie F. Paper Foundation, Joseph Paper, President.

†Tubadil, purified d-tubocurarine chloride pentahydrate, 25 mg. per cubic centimeter in a menstruum of peanut oil, oxycholesterol, and beeswax—Endo Products, Inc.

nificant differences could be found between the control or drug groupings. In Table I a chi square test in the multiparous group, comparing numbers of episiotomies, shows a significant difference between the control and the Tubadil group (p. = .02). In all other instances no significant differences could be determined.

Certain trends are of course apparent from the data. In Table II there appears to be a reduction in the required number of forceps deliveries in the Tubadil group. Table III suggests that more babies were delivered faster following Tubadil injection, although this applies only to those delivered during the first 2 hours after Tubadil injection. From Table IV there appears to be no discernible change in the amounts of medication required for analgesia in the two groupings. Table V indicates to us the safety of the medication used.

TABLE I. EPISIOTOMIES AND PARITY

	PRIMIPAROUS		MULTIPAROUS		ALL PARITIES
	NO. OF PATIENTS	EPISIOTOMIES	NO. OF PATIENTS	EPISITOMIES	TOTAL EPISITOMIES
Control	34	33	66	52	85
Tubadil	25	24	75	47	71

TABLE II. FORCEPS, LACERATIONS, POSTPARTUM HEMORRHAGE, AND CATHETERIZATION

		FORCEPS APPLIED	LACERATIONS	POSTPARTUM HEMORRHAGE OVER 250 C.C.	POSTPARTUM CATHETERIZATION
Control	100	21	5	7	5
Tubadil	100	17	9	9	4

TABLE III. TIME FROM INJECTION OF TUBADIL OR CONTROL MEDICATION TO DELIVERY OF INFANT

		0-2 HOURS	2-4 HOURS	4-6 HOURS	6-8 HOURS	8-10 HOURS	10-12 HOURS	12+ HOURS
Control	100	40	32	12	3	7	3	3
Tubadil	100	47	31	7	7	2	5	1

TABLE IV. DOSAGE OF ANALGESICS REQUIRED

		BARBITURATES		DEMEROL		SCOPOLAMINE	
		100 MG. OR LESS	MORE THAN 100 MG.	100 MG. OR LESS	MORE THAN 100 MG.	1/100 GRAIN OR LESS	MORE THAN 1/100 GRAIN
Control	100	13	5	63	32	59	19
Tubadil	100	14	12	68	29	75	8

TABLE V. VITAL STATISTICS AND NEED FOR RESUSCITATION

		STILLBIRTHS	LIVE BIRTHS	SPONTANEOUS RESPIRATIONS	RESUSCITATION	NEONATAL MORTALITY
Control	100	1	99	98	1	0
Tubadil	100	0	100	99	1	0

Summary

1. A carefully controlled study of 200 normal obstetrical patients alternately given a placebo or an injection of repository curare showed no signifi-

cant differences between the two groupings. An exception is noted in that there was a significant reduction in the number of episiotomies in the multiparous patients, when the Tubadil series is compared with the control series.

2. There were no harmful effects on mother or child with the preparation used.

3. The further use of repository curare in routine obstetrics is not justified from this report.

References

1. Lipow, E. G.: A. M. A. Arch. Surg. **66**: 312, 1953.
2. Lenahan, N. E., and Hamilton, W. H.: Current Res. in Anesth. & Analg. **32**: 206, 1953
3. Johnson, L. J., and Schilla, F. W.: Am. J. Surg. **83**: 33, 1951.
4. Fuller, J. D.: J. A. M. A. **194**: 789, 1950.
5. Hobach, W. W.: J. Tennessee M. A. **45**: 16, 1952.
6. Laborit, H., Valla, G., Le Lamar, A., and Vogel, L.: Gynéc. et obst. **47**: 585, 1948.
7. Katzman, H., Friedman, J. M., Katzman, S., and Dodek, S. M.: M. Ann. District of Columbia **18**: 561, 1949.
8. Hartnett, L. M., and Freiheit, H. J.: South. M. J. **43**: 277, 1950.
9. McMann, W.: Am. J. Obst. & Gynec. **60**: 1366, 1950.
10. Jewell, T. C.: Am. J. Obst. & Gynec. **67**: 273, 1954.
11. Cohen, E. N., Bernstein, W. C., and Elert, B.: Current investigation to be published

APPLICATIONS OF THE RESERVE MIDGET MACHINE IN OBSTETRICAL ANESTHESIA

Preliminary Report*

VINCENT TRICOMI, M.D., DAVID P. BAUER, M.D., AND
LOUIS M. HELLMAN, M.D., BROOKLYN, N. Y.

(From the Department of Obstetrics and Gynecology, State University of New York College of Medicine at New York City and the Kings County Hospital)

SINCE March of 1954 a portable, light-weight machine, called the Reserve Midget, has been employed for the induction of anesthesia and for the conduction of short anesthesia at the University Hospitals of Cleveland. A preliminary report by Dr. Robert Hingson[1] concerning its use appeared in the Oct. 9, 1954, issue of *The Journal of the American Medical Association.* Interestingly, the machine had been applied to the field of obstetrics; in fact, it was first used for inducing surgical anesthesia in a multiparous patient whose first stage of labor terminated sooner than expected; induction was obtained with three breaths. In light of this, we decided to evaluate it as a possible addition to the already vast, though controversial, armamentarium of obstetrical anesthesia. Our experience with 63 consecutive obstetrical patients at the Kings County Hospital constitutes the theme of the present report.

The machine (Fig. 1) weighs 482 Gm. and measures 63 cm. in length. It consists of the following parts: (a) a rubber conductive face mask; (b) a spark-proof aluminum central axial body with a compression spring valve that may be opened and closed with slight pressure; (c) a conductive and transparent soda lime canister; (d) two right arm aluminum containers to hold the gas cylinders; (e) gas cylinders; (f) a 6 L. conductive rebreathing bag with a distal nipple port whereby the bag may be connected to reservoir or wall oxygen for sustained procedures.

The seals on the gas-filled cylinders are perforated by a specially designed perforating and sealing mechanism after they are in place in the side arm containers. This is effected by screwing the side arm container to the axial body. A safety device precludes the inadvertent and simultaneous placement of two cylinders of anesthetic gases into the machine to the exclusion of an oxygen cylinder. This device is a reversal of the pin index system used in standard anesthetic machines. By means of such a safety device, it is possible to use only one anesthetic and one oxygen cylinder at the same time. After the cylinder seals are punctured in sequence by the perforating mechanisms, the directional baffle of the central axial body shunts the gas flow into the rebreathing bag; slight pressure on the compression spring then opens the ports from the rebreathing bag to the mask and patient, permitting the exchange of gases within the unit.

*Presented at a meeting of the Kings County Medical Society, May 17, 1955.

Although several anesthetic gases have been packaged, our experience has been limited to the oxygen-helium and cyclopropane-helium combinations. Table I shows both the total volume of free gases and the percentages of gases present at the beginning of an induction when one cylinder of oxygen-helium and one cylinder of cyclopropane-helium are used.

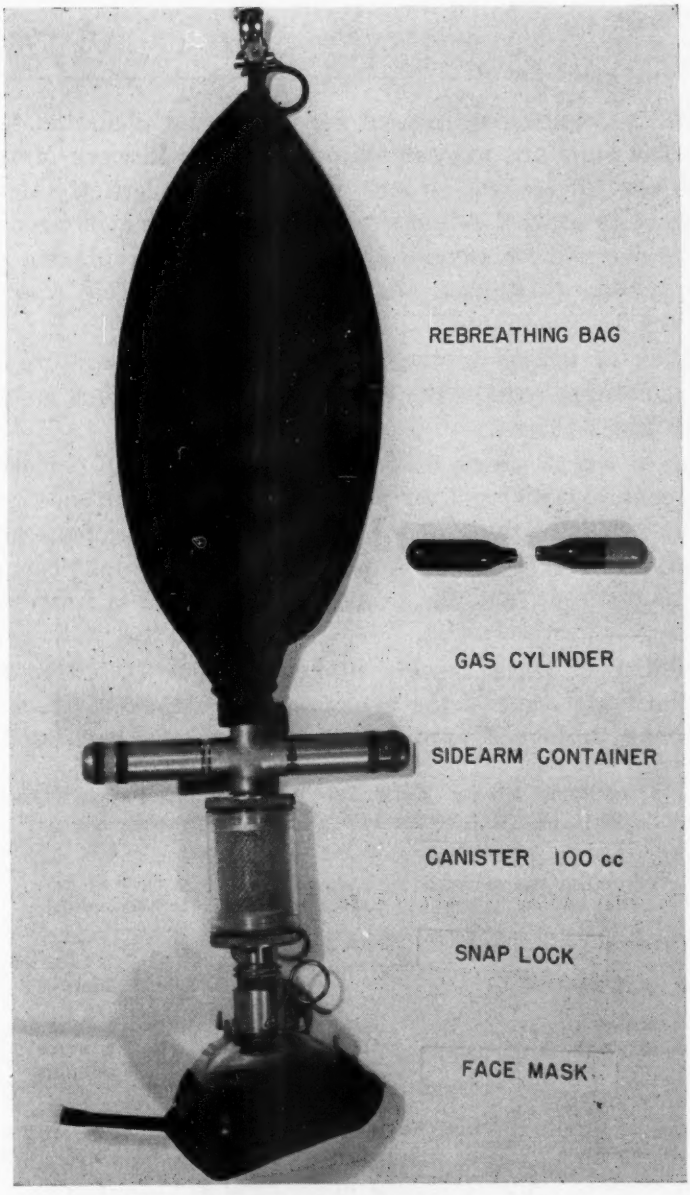


Fig. 1.—Hingson Reserve Midget machine.

The amount of cyclopropane in the standard cylinder, 2,200 c.c., weighs 4,050 mg. Since the average patient, with a blood volume of about 6,000 c.c., requires 960 mg. of cyclopropane to obtain Stage III, Plane 2 anesthesia, the amount of cyclopropane stored in each cylinder is sufficient to produce anesthesia through primary blood stream saturation.

TABLE I. INITIAL GASEOUS CONSTITUTION IN THE REBREATHING BAG

GAS	VOLUME (C.C.)	PERCENTAGE
Combination 1.—		
Cyclopropane	2,200	40
Helium	1,180	
Combination 2.—		
Helium	470	30
Oxygen	1,650	30

The patient's volume requirement for oxygen is calculated to be 300 c.c. per minute. The standard oxygen cylinder for the Reserve Midget machine contains 1,650 c.c. Therefore, to stay within the margin of safety, we have limited the use of an oxygen cylinder to 5 minutes. One cyclopropane cylinder may be used to every three oxygen cylinders. By also replacing the depleted cyclopropane cylinders, Hingson has been able to maintain a surgical plane of anesthesia for forty minutes.

The addition of helium to the cyclopropane-oxygen mixture, by diluting the explosive molecules, reduces the explosive potential approximately two hundred and forty times (Fig. 2).

The graph in Fig. 2 shows that the combination of 40 per cent cyclopropane, 30 per cent oxygen, and 30 per cent helium is within the noninflammable range and remains there as the oxygen and cyclopropane are taken up. At the end of the five minutes the concentration of cyclopropane is never greater than 20 per cent, and the proportion of helium is between 60 and 70 per cent.

The possibility of going beyond Stage III, Plane 3, within five minutes is slight, as the body absorbs the cyclopropane. If, however, ventilation is inadequate during prolonged application, Plane 3 may be passed.

TABLE II. ANESTHETIC EFFECT WITH AND WITHOUT PREOPERATIVE ANALGESIA

Number of Cases		63
Multiparas		40
Number of patients who had analgesia (15—109 minutes before anesthesia)		32
Average number of breaths to Stage III, Plane 2	8.4	(5—18)
Average duration of anesthesia	5.7	(1—15 minutes)
Without analgesia		10.8 minutes
With analgesia		12.5 minutes
Average		11.6 minutes

In the series of 63 obstetrical patients managed with the Hingson machine, 40 were multiparas and 23 were primiparas. Of these, 55 were delivered. The remaining 8 underwent miscellaneous obstetrical manipulations. Thirty-two patients had been given analgesic drugs from 15 to 109 minutes prior to the inhalation of the cyclopropane-oxygen-helium mixture (Table II).

Hingson states that from 6 to 12 breaths provide surgical anesthesia. In this series, the average number of breaths to Stage III, plane 2, was 8.4, with a range of from 5 to 18 breaths. The average duration of anesthesia was 5.7 minutes with the span ranging from one to fifteen minutes.

Since induction was so rapid, the duration of anesthetic effect was computed from the time the patient began to breathe the anesthetic mixture until the time she first reacted to painful stimulation. The average duration of anesthetic effect was 10.8 minutes for the patients who had not received analgesia and 12.5 minutes for those who had analgesia.

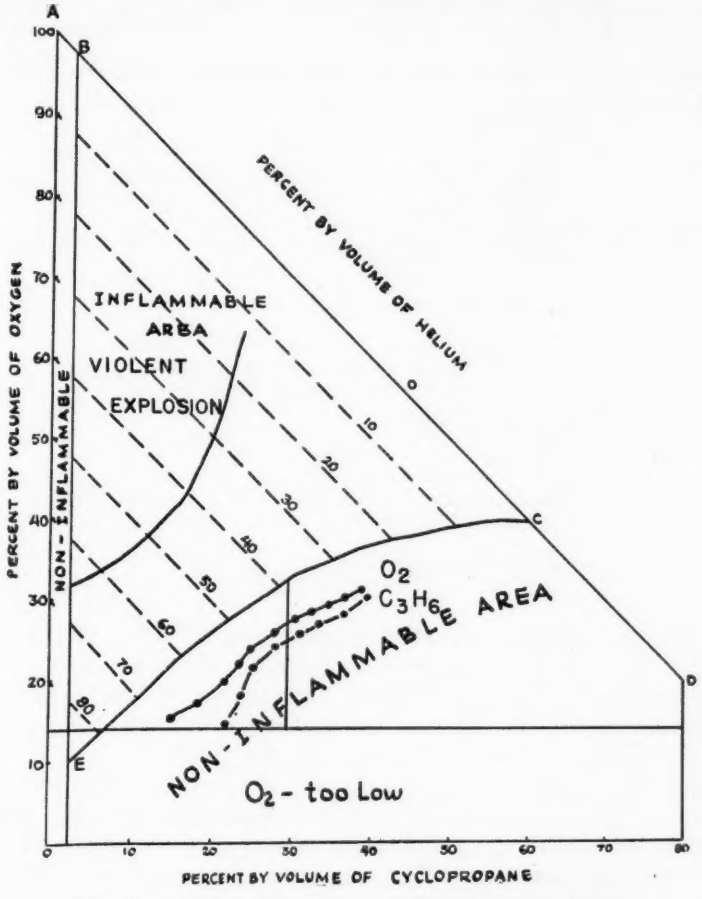


Fig. 2.—Inflammable range of the gaseous mixture.

TABLE III. BREATHING AND CRYING TIME

Breathing Time.—	
Without analgesia	44.0 seconds
With analgesia	58.3 seconds
Average	51.1 seconds
Crying Time.—	
Without analgesia	45.8 seconds
With analgesia	53.8 seconds
Average	49.8 seconds

The fully established breathing and crying times of the newborn infants are compared in Table III and related to whether the mother did or did not have analgesia.* There is little difference between the two groups and the average of each is not remarkable.

*In this study, breathing and crying times were taken when they were fully established; usually only the time of the first breath and cry are recorded.

Stated otherwise, however, 22 per cent of the newborn infants had a breathing time of more than one minute and 11 per cent had a crying time of greater than 2 minutes. Hellman recently reported an average of 7.3 per cent of infants with poor breathing response whose mothers had an encephalic approach to pain relief at delivery. The percentage of infants with poor crying time was the same in both studies.

TABLE IV. OBSTETRICAL MANIPULATIONS AND COMPLICATIONS

Operations.—	
Spontaneous	22
Low forceps	26
Midforceps	2
Piper forceps	1
Assisted breech	3
Pelvic examination	1
Episiotomy	32
Episiotomy with repair	12
Manual removal of placenta	33
Version and extraction (term infant)	1
Breech extraction (second twin)	1
Complications.—	
Laryngospasm, transient, mild	7
Postanesthetic vomiting	4
Postanesthetic headache	1
Reached Stage II only	1
Cardiac complications	0

Table IV lists the obstetrical manipulations effected in the present series of cases; the total number exceeds 63 because some patients underwent two or more procedures. The procedures undertaken do not necessarily reflect departmental policy at the Kings County Hospital; rather, they were directed at testing the efficacy of the new anesthetic machine.

An effort was made to record all complications. Seven patients had mild and transient laryngospasm which did not require therapeutic measures. Four patients had postanesthetic vomiting and one patient had a mild and transient postanesthetic headache. In only one instance was Stage III not reached. There were no cardiac complications.

TABLE V. EVALUATION OF RESULTS

Subjective Response.—	
Excellent	61
Good	2
Poor	0
Objective Response.—	
Excellent	58
Good	4
Poor	1

The ratio of cyclopropane-helium cartridges to oxygen-helium cartridges employed, for the entire series, was 1 to 2.

Subjectively, 61 patients reported an excellent response and 2 a good response. Objectively, we considered 58 patients to have had an excellent response, 4 a good response, and one a poor response (Table V).

Summary

A series of 63 consecutive obstetrical patients managed with the Hingson Reserve Midget machine is presented. The study is too small to arrive at any definitive conclusion. It appears, however, that this compact unit may merit a place in the field of obstetrical anesthesia. The machine is easy to handle and explosion hazards are markedly reduced. Despite these advantages the dangers inherent in the administration of any and every anesthetic agent remain.

References

1. Hingson, R. A.: J. A. M. A. **156**: 604, 1954.
2. Hingson, R. A.: Personal communication, 1955.
3. Hellman, L. M.: Factors Influencing the Choice of Anesthetic and Analgesic Methods in Obstetrical Practice, Seminar, Sharp & Dohme, **16**: 1, pages 3-9, 1955.

HISTOGENESIS OF DEGENERATIVE PROCESSES IN THE NORMAL MATURE PLACENTA*

ROBERT BURSTEIN, M.D., FRED P. HANDLER, M.D., SAMUEL D. SOULE, M.D., AND HERMAN T. BLUMENTHAL, M.D., ST. LOUIS, MO.

(From the Departments of Obstetrics and Gynecology, The Jewish Hospital and Washington University School of Medicine, and the Department of Pathology, The Jewish Hospital)

IT HAS become customary to consider the developmental changes in the placenta during its 9 months of intrauterine existence as an accelerated aging process in an organ with a short life span. Thus Grosser,[15] Young,[30, 31] Bartholomew and co-workers,[2-5] Eden,[11] Fraser,[12] Williams,[29] Tenney and Parker,[26, 27] and others have reached such a conclusion on the basis of histological evidence which includes an increased fibrosis of villi, deposition of fibrin, formation of infarcts, loss of the Langhans cell layer, and endarteritis. Further evidence supporting an aging concept has been presented by Wang and Hellman,[28] who observed a progressive decrease in oxygen consumption per gram of placenta, and in the studies of Mandel, Graff, and Graff,[19] who found that the changes in nucleo-cytoplasmic ratio of placentas of various ages followed a decreased logarithmic curve similar to that established for age and rate of growth of various other tissues.

On the other hand, Smith and Kennard,[23] Cohen, Marrian, and Watson,[10] Probstner,[21] and others have observed that the quantities of estrogen and progesterone presumably produced by the placenta reach their highest levels at term, and Gellhorn and Flexner[13] have reported that the rate of transfer of radioactive sodium per gram of placenta is increased sixfold from the twelfth to the fortieth week of pregnancy. Such data show an increasing rather than a decreasing physiological activity with advancing age of the placenta.

As regards degenerative vascular lesions and complications which may be attributed to them in relation to an aging concept, Ackermann[1] was the first to direct attention to "endarteritis" of the fetal vessels of the placenta. Eden,[11] Williams,[29] and others confirmed this finding and such observations led to the concept that occlusion of the large fetal vessels produced an ischemia, followed by infarct formation and fibrin deposition. Bartholomew and co-workers[2, 4] have specifically stressed the histological and pathogenic resemblance of the vascular lesions in the placenta to atherosclerosis in the adult human coronary artery and to the experimentally produced hypercholesterolemic lesion in arteries of the rabbit.

Opposed to the concept of impairment of fetal vascular supply are the observations of Young,[30, 31] Strachan,[25] Siddall,[22] and Stander,[24] which favor

*These investigations were supported by a grant from the Francis Israel Fund of the Noshin Rachmonioth Society of St. Louis.

instead impairment of maternal nutrition to the placenta. Novak[20] has reviewed the evidence opposing the concept of fetal vascular lesions as the primary etiological factor in degenerative changes in the placenta, and has pointed out particularly that ischemic necrosis of a villus is due to fibrin encasement which excludes it from the maternal circulation and not to occlusion of fetal vessels. He considers the syncytial covering of villi as analogous to the endothelial lining of blood vessels, and the changes in this covering comparable to the formation of intimal plaques.

It is apparent from the foregoing that both concepts dealing with the pathogenesis of degenerative changes in the placenta are based on the development of lesions resembling adult arteriosclerosis either within the fetal component of the placental circulation or about the syncytial covering of the villi. If such lesions are truly comparable to adult arteriosclerosis and develop at an accelerated rate, then the placenta would afford an excellent source of material for studies of a more general character dealing with degenerative vascular disease. The latter consideration led to this study of the vascular histology of the placenta utilizing methods which were previously employed in investigations dealing with vascular disease in other locations,[6-8, 14, 16, 18] in order to evaluate resemblances to and differences from adult arteriosclerosis. A comprehensive study of this type might also be expected to serve as a reference point for subsequent investigations on vascular changes in spontaneous abortion, prematurity, toxemia, and other complications of pregnancy.

Material and Method

Placentas were collected from 50 term pregnancies in which the prenatal period and the course of labor were entirely normal. A segment of umbilical cord approximately 1.5 cm. in length and a peripheral wedge of placenta measuring 1.5 by 2.5 cm. were excised from each specimen. These were fixed in alcohol-formalin (one part 40 per cent formaldehyde and 9 parts 95 per cent ethyl alcohol) to minimize loss of water-soluble minerals which would impair specimens for microincineration studies. Successive sections of cord and placenta were stained with hematoxylin and eosin, with the Weigert-Verhoeff stain for elastic tissue, with a modified periodic acid-Schiff (PAS) stain for mucopolysaccharide, and with the van Gieson technique for connective tissue and muscle. One section was also microincinerated for dark-field study of mineral distribution.

Results

Umbilical Cord.—The two arteries of the umbilical cord showed a thick wall consisting of two distinct strata of muscle and a thin intima (Fig. 1). The inner surface was invariably covered by a single layer of endothelial cells. In most instances the endothelium lay directly on the inner muscle layer; in a few instances elongated connective-tissue cells separated endothelium from muscle, but in no instance did this subendothelial layer exceed 10 per cent of the thickness of the wall either locally or diffusely. Thin bands of PAS-positive material more consistently separated endothelium from inner muscle. In all of the umbilical arteries there was either a complete absence of an internal elastic membrane or only a rudimentary one was present consisting of focal collections of a few elastic filaments. When present such elastic filaments lay between endothelium and inner muscle layer, or within inner

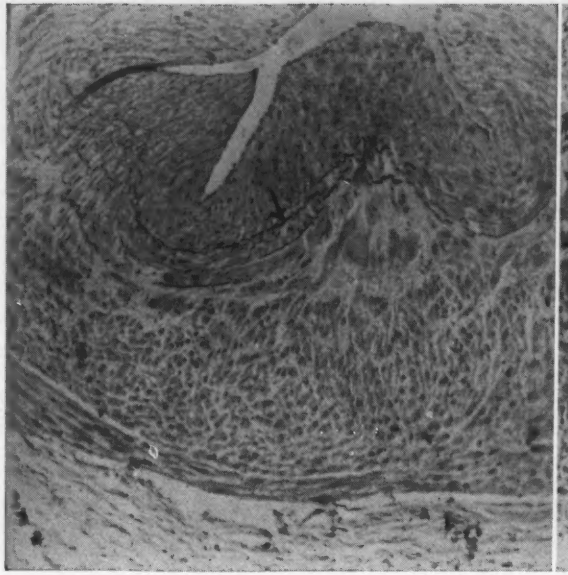


Fig. 1.

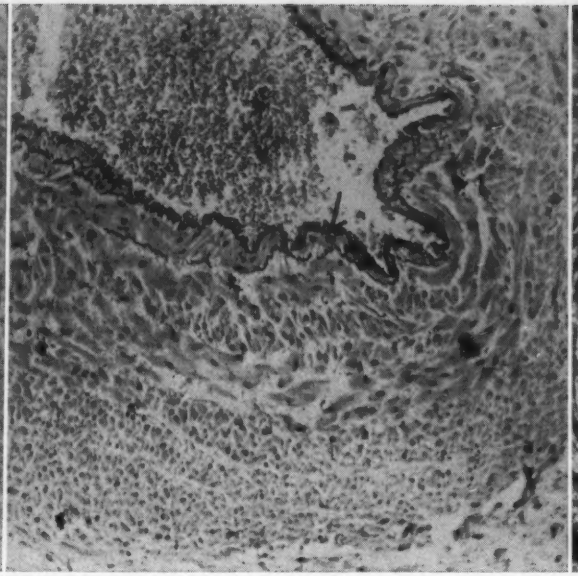


Fig. 2.

Fig. 3.

Fig. 1.—Umbilical artery, Weigert-Verhoeff stain. Arrow shows elastic filaments separating two layers of muscle. There is no continuous internal elastic lamella. (Approximately ×100; reduced ⅙.)

Fig. 2.—Umbilical vein, Weigert-Verhoeff stain. Note single layer of muscle; arrow indicates continuous internal elastic lamella. There are additional elastic fragments in the superficial media. (Approximately ×100; reduced ⅙.)

Fig. 3.—Umbilical artery, microincineration. There is a normal nuclear distribution of mineral ash. (Approximately ×100; reduced ⅙.)

muscle layer. The inner stratum of smooth muscle appeared to have a spiral arrangement; it gave a less eosinophilic staining reaction than the outer layer because of a looser arrangement of muscle fibers which were separated by PAS-positive ground substance. The outer muscle zone had a circular arrangement similar to that usually seen in the media of muscular arteries; the muscle fibers were intensely eosinophilic and compactly arranged, with scant intervening ground substance. Occasionally scattered elastic filaments were noted between muscle fibers of the inner zone or in focal collections between the two muscle strata. The adventitia which consisted of a thin layer of loosely arranged connective-tissue cells was consistently devoid of any elastic elements which might constitute even a rudimentary external elastic lamella.

The single umbilical vein more closely resembled an artery in structure than did the two arteries (Fig. 2). As in the latter there was always a single layer of endothelial cells lining the inner surface. Unlike the arteries, the vein uniformly showed a well-developed intact internal elastic membrane, usually separated from the endothelium by a thin layer of PAS-positive fibers. The media consisted of a single stratum of circularly arranged smooth-muscle fibers; the latter were usually compactly grouped and only occasionally separated by ground substance. As in the arteries, there was no evidence of even a rudimentary external elastic membrane.

Microincinerated sections of umbilical cord showed fine calcium granules in the nuclei, cell membranes, and ground substances. The concentration of minerals in arteries (Fig. 3) and vein was no greater than that observed in various major arteries of newborn infants.

Placenta.—Arterial as well as venous channels of all sizes in the placenta were lined by a single layer of endothelium. Generally there was no subendothelial connective tissue, but fibrils of PAS-positive material formed a subendothelial band; the latter was present in this location in all vessels, but was more marked in the arterial than in the venous system down to and including the capillaries. There was no appreciable intimal thickening and plaque formation was never encountered. Unlike the umbilical arteries, even the largest channels in the placental arterial circulation showed no evidence of stratification of the muscular wall; the latter consisted of a single stratum of circularly arranged muscle fibers which appeared hypertrophied and were compactly arranged (Fig. 4). This hypertrophy was present in arteries of all calibers including arterioles; at times it was so pronounced that the lumina of the vessels appeared narrowed. There were occasional collections of connective-tissue cells and/or PAS-positive bands which separated muscle fibers. Veins could be distinguished from arteries only by their thinner muscle layer.

Microincinerated specimens showed a mineral distribution in placental arteries similar to that seen in umbilical vessels (Fig. 6). However, calcium deposition of greater intensity was observed in the placental plate (Figs. 7 and 8), in supporting trabeculae (Fig. 6) and in degenerating syncytial knots of the villi (Fig. 9).

Because the surface covering of villi has been considered comparable to the endothelium of blood vessels,[20] the villi were studied from the point of view of determining whether or not plaquelike lesions developed just beneath the surface and extended into adjacent supporting structures. Two distinct types of villi were noted, differing prominently in the characteristics of the supporting stroma. The first contained a compact cellular fibrous stroma and this type usually showed pronounced syncytial bud formation. The second type contained a loose myxoid stroma and the covering showed intact sheets of epithelium interrupted only occasionally by syncytial buds. Nothing comparable to plaque formation was seen beneath the surface of villi. Many of

Fig. 4.

Fig. 5.

Fig. 6.

Fig. 4.—Supporting trabecula, hematoxylin and eosin. Artery shows a markedly hypertrophied medial coat with small lumen. (Approximately ×100; reduced ⅙.)

Fig. 5.—Supporting trabecula, Weigert-Verhoeff stain. This section shows hypertrophied arteries without elastic tissue similar to that in Fig. 4. Along the right side, beneath the acellular fibrinoid mass, arrow indicates a wavy black elastic filament. Note syncytial covering of fibrinoid mass which is continuous with syncytium where fibrinoid is absent. (Approximately ×100; reduced ⅙.)

Fig. 6.—Supporting trabecula, microincineration. The mineral ash pattern of the matrix and arteries is nuclear, but there is a continuous white subsyncytial line (arrow) corresponding to elastic fiber. (Approximately ×100; reduced ⅙.)

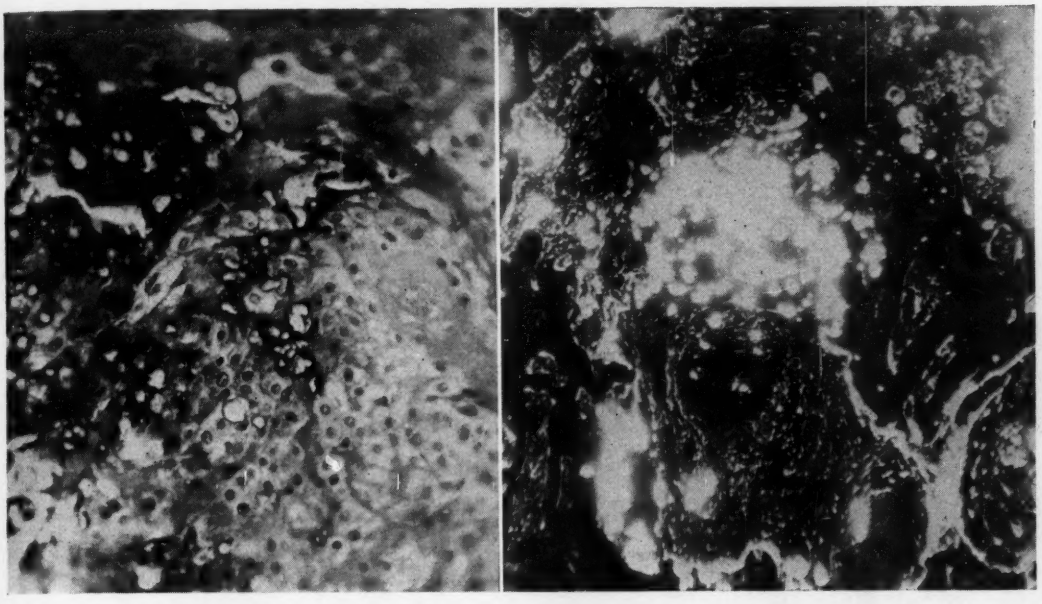


Fig. 7. Fig. 8.

Fig. 7.—Decidual plate, hematoxylin and eosin. Section shows intense calcification of decidual cells. (Approximately ×100; reduced ⅙.)

Fig. 8.—Decidual plate, microincineration. Heavy mineral ash deposit corresponds to intense calcification in Fig. 7. (Approximately ×100; reduced ⅙.)

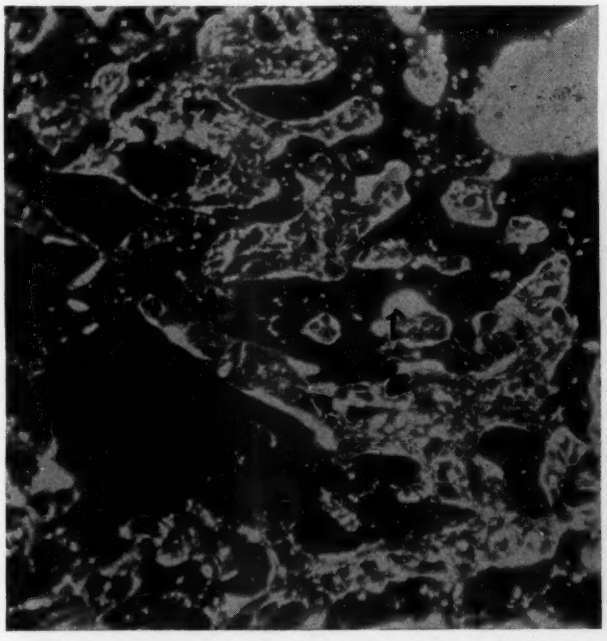


Fig. 9.—Small villus, microincineration. Arrow indicates calcification of a syncitial knot. (Approximately ×100.)

Fig. 10.

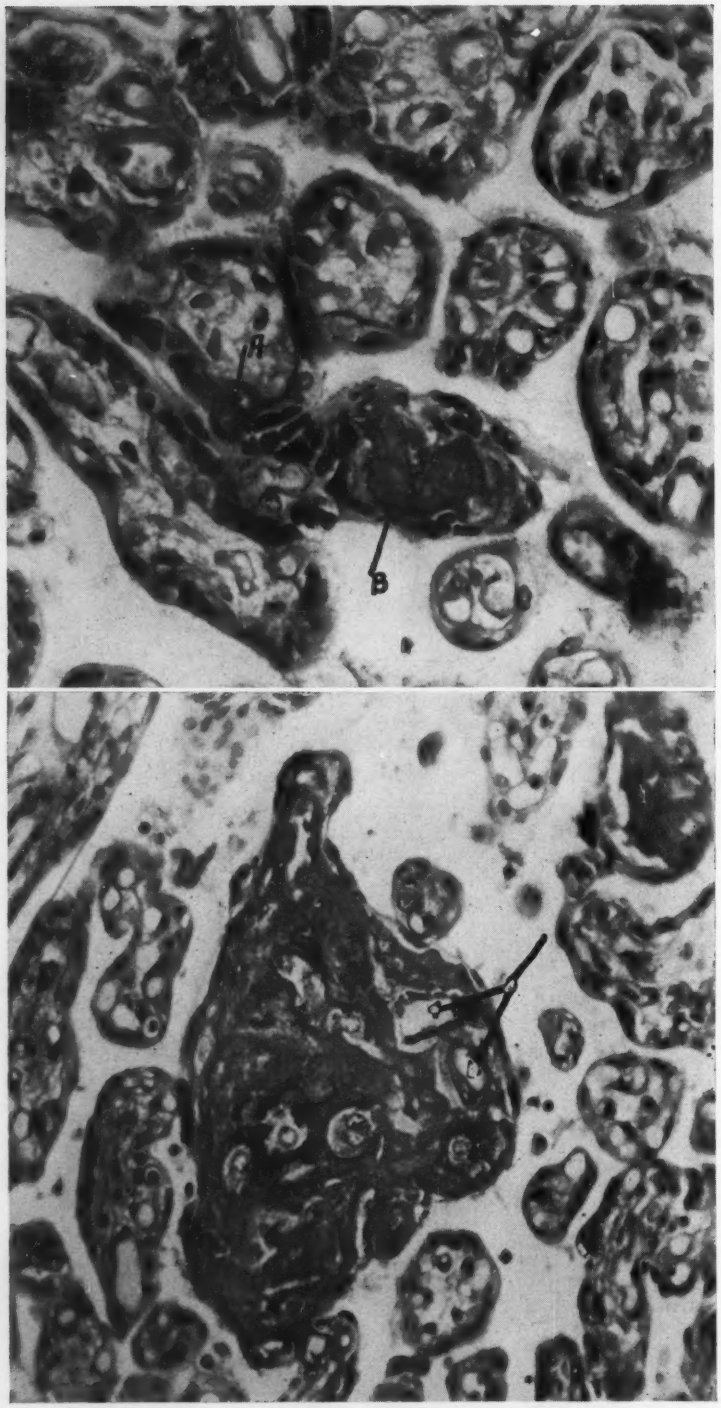


Fig. 11.

Fig. 10.—Placental villi, periodic acid-Schiff stain. One small villus is almost completely replaced by fibrinoid which is completely surrounded by intact syncytium (Arrow *B*). Adjacent is a villus showing a small fibrinoid deposit which interrupts the continuity of the PAS-positive epithelial basement membrane (Arrow *A*). (Approximately ×150.)

Fig. 11.—Placental villi, periodic acid-Schiff stain. A large central villus is almost completely replaced by fibrinoid which is surrounded by intact syncytium. Within the fibrinoid mass, however, there remain a few viable cells and patent capillaries (double arrow). (Approximately ×150.)

the latter, as well as supporting trabeculae, however, showed deposits of a homogeneous granular material resembling fibrin in hematoxylin and eosin stained specimens; this material gave an intensely positive reaction with the PAS stain. Such fibrinlike deposits were seen in villi in many areas in which true fibrin was not deposited on the surface of the villus. From a careful study it appeared that the PAS-positive material first appeared in the connective-tissue stroma of villi as an extension from the epithelial basement membrane (Fig. 10), where it progressively increased in quantity eventually to replace completely the supporting connective tissue (Figs. 5 and 11) and break through the attenuated covering epithelium to fill the intervillous space. This process was so extensive in some regions as to give the appearance of an infarct. Careful study, however, frequently disclosed clusters of apparently viable cells even in areas where this process was marked and, in some villi so involved, patent, apparently normal blood vessels could be identified. Nowhere was it possible to identify occluded, thrombosed, or otherwise abnormal vessels to which this process might be attributed, although undoubtedly some vessels were replaced by fibrinoid deposit.

In some supporting trabeculae of the placenta, elastic fibrils were found beneath the epithelium or beneath a layer of PAS-positive material lying immediately subjacent to the covering epithelium (Fig. 5). In 6 cases (12 per cent) this process was marked and in 17 cases (34 per cent) it was graded as mild. These filaments showed an affinity for calcium comparable to that observed in the elastic tissue of adult arteries (Fig. 6).

Comment

As has been previously pointed out the arteriosclerotic process shows considerable variability depending upon the anatomical location and related hemodynamic factors, as well as the basic histological structure of the artery involved.[6-8, 14, 16, 18] Where intimal plaques develop, the process initially consists in the laying down of fibroelastic tissue beneath the endothelial layer; this process is accompanied by changes in ground substance and by splitting and fraying of the internal elastic lamella. In many arteries there is a progressive calcification of the elastic elements in this region and later lipids appear at the base of intimal plaques. In elastic arteries such as the aorta and its major branches the medial elastic tissue also undergoes progressive calcification. In some muscular arteries such as the renal and splenic, degenerative changes in the medial muscle with calcification are frequently found. Finally, while in most arteries which have an external elastic lamella reduplication and calcification of this layer are minimal to moderate, in the renal artery such processes become quite marked with advancing age.

It is apparent from the foregoing that we have not observed comparable processes in the fetal vessels of the placenta. The latter are completely devoid of elastic elements, show no evidence of formation of plaques with deposition of lipids, and microincinerated sections show no evidence of calcium deposition in abnormal amounts. As regards the development of lesions resembling arteriosclerosis along the covering of villi, except for calcification of degenerating syncytial knots, there is again no resemblance to adult arteriosclerosis.

In the full-term normal placenta we have therefore been unable to demonstrate occlusion of fetal vessels, nor have we observed evidence of traumatic

injury to large fetal vessels as suggested by Bartholomew and Kracke.[2] The only vascular peculiarity which was found was the relatively excellent state of development of medial muscle in the arteries of both the umbilical cord and the placenta. This appears to be a response to hormonal stimuli of the same type as that which occurs in the media of uterine vessels. While in such hypertrophied arteries the lumen appears relatively small, there is no evidence of intimal disease and it appears most likely that the lumen is of adequate caliber, but that the increased muscular thickness alters the ratio of the diameter of the lumen to the thickness of the wall.

The absence of elastic elements in the arteries of the placenta and their rudimentary state of development in the umbilical arteries is noteworthy. In connection with a study of pulmonary arteries,[14] the importance of intravascular pressure as a stimulus to the new formation of elastic tissue was suggested, and is under investigation. Since the operating pressure of fetal arteries is quite low (40 to 60 mm. Hg), it may be that such a stimulus to the formation of elastic elements is lacking in the placenta. In the umbilical vessels the pressure which obtains may be marginal, since rudimentary elastic filaments are formed in this location. Oxygen tension may also be of importance, however, since the umbilical vein showed a better developed internal elastica than did the arteries.

There remains to be accounted for the presence of elastic fibrils in the supporting trabeculae which is also not yet clearly understood. This may again bear some relation to the pulsations of large arteries against the supporting connective tissue of these columns. Further study of placentas from abnormal pregnancies may make it possible to define more clearly factors which stimulate the development of elastic elements.

As Novak[20] has noted, there is at the present time considerable confusion regarding the use of the term "infarction." An infarct in general pathology refers to massive necrosis of tissue resulting from obstruction of circulation to the area, and is usually due to atheromatous occlusion, thrombosis, or embolism. It is apparent from the foregoing that this is not the case in the mature normal placenta, and, even if thrombosis should occasionally occur, a collateral circulation, in a sense, exists in the form of maternal blood sinuses from which diffusion into villi could occur. Similarly, the coating of the surface of a villus by fibrin isolating it from the maternal circulation does not constitute a valid explanation of infarction, since then the fetal circulation could serve as a collateral blood supply. We therefore agree with Clemens[9] that the term infarct as referred to placental degeneration is not applicable.

From our observations it is highly questionable whether massive necrosis commonly occurs as such in normal term placentas. Careful study of the PAS-stained specimens has shown a progressive increase in a PAS-positive substance, presumably a mucopolysaccharide, in villous connective tissue even in areas where no overlying fibrin deposits were present. This material appears to be a product of connective-tissue metabolism. It may progress to the point of completely replacing the connective-tissue stroma of villi and produce marked attenuation and even rupture of the overlying syncytial layer, thus spreading

into the maternal sinuses. This may in turn result in fibrin deposition from maternal blood. As adjacent areas in which this process occurs become contiguous, the superficial appearance of massive necrosis results. This we have referred to as "pseudoinfarction." We agree with Hitschmann and Lindenthal[17] in designating this process as "fibrinoid degeneration" in contradistinction to fibrin deposition on the surface of villi from maternal sinusoidal blood. The two processes may occur concomitantly in the same area and are indistinguishable histochemically at the present time; but they do not appear to be directly related to each other. Since we have been unable to establish a circulatory basis to account for fibrinoid degeneration, it appears most likely that this is a connective-tissue response to hormonal stimulation, although changes in permeability of the syncytial layer may also play a role.

Such a hypothesis is based primarily on the likelihood that this is a process of increasing intensity with progressive maturation of the placenta which parallels the increase in circulating estrogen and progesterone levels as well as the increase in permeability of the syncytial layer of the villi. This hypothesis is being pursued on an experimental basis. It is important to obtain an understanding of the pathogenesis of these degenerative changes in order properly to interpret metabolic studies of placental tissues. Thus diminished metabolic activity of any type per gram of tissue must be related to loss of cells and replacement by an acellular material probably incapable of active metabolism.

While vascular changes appear to play no important role in the development of degenerative changes in the normal term placenta, lesions of blood vessels may develop in pathological states associated with pregnancy in which case they may play a contributory role in intensifying these degenerative processes. Apparently many of the conclusions drawn by previous investigators regarding vascular degeneration in the normal term placenta have been based on observations on pathological placentas in which the lesions observed were interpreted as presenting an intensification of processes which occur in the normal organ. A study of placentas in abnormal pregnancy states is in progress for the purpose of determining the nature of the vascular changes and of evaluating their role in degenerative processes in the placenta.

Summary

The umbilical cords and placentas obtained from 50 normal pregnancies have been studied by various histochemical techniques used in previous investigations dealing with degenerative processes in adult vessels. It has been shown that the basic structure of umbilical and placental arteries is different from adult arteries particularly with regard to the paucity or complete absence of elastic elements as well as the state of development of medial muscle.

It has been further demonstrated that degenerative processes which occur in the normal term placenta are apparently not on a vascular basis, but rather on the basis of intrinsic connective-tissue changes probably due to hormonal influences. Such degenerative changes should therefore not be considered infarcts, despite certain superficial gross and microscopic resemblances to the

latter. A fibrinoid material deposited in progressively increasing amounts within villi appears to constitute the basic process by which such pseudoinfarcts develop.

We wish to express our appreciation to the House Staffs of St. Louis Maternity Hospital and the Department of Obstetrics of the Homer G. Phillips Hospital for their assistance in obtaining some of the specimens utilized in this study.

References

1. Ackermann, Prof.: Virchows Arch. path. Anat. **96**: 439, 1884.
2. Bartholomew, R. A., and Kracke, R. R.: AM. J. OBST. & GYNEC. **24**: 797, 1932.
3. Bartholomew, R. A., and Parker, F.: AM. J. OBST. & GYNEC. **27**: 67, 1934.
4. Bartholomew, R. A., and Colvin, E. D.: AM. J. OBST. & GYNEC. **36**: 909, 1938.
5. Bartholomew, R. A.: J. A. M. A. **111**: 2276, 1938.
6. Blumenthal, H. T., Lansing, A. I., and Wheeler, P.: Am. J. Path. **20**: 665, 1944.
7. Blumenthal, H. T., Lansing, A. I., and Gray, S. H.: Am. J. Path. **26**: 989, 1950.
8. Blumenthal, H. T., Handler, F. P., and Blache, J. O.: Am. J. Med. **17**: 337, 1954.
9. Clemens, E.: Ztschr. Geburtsh. u. Gynäk. **84**: 758, 1922.
10. Cohen, S. L., Marrian, G. F. and Watson, M.: Lancet **1**: 674, 1935.
11. Eden, T. W.: J. Path. & Bact. **4**: 265, 1897.
12. Fraser, J.: AM. J. OBST. & GYNEC. **6**: 645, 1923.
13. Gellhorn, A., Flexner, L. B., and Hellman, L. M.: AM. J. OBST. & GYNEC. **46**: 688, 1943.
14. Gray, S. H., Handler, F. P., Blache, J. O., Zuckner, J., and Blumenthal, H. T.: Arch. Path. **56**: 238, 1953.
15. Grosser, O.: Frühentwicklung, Einhautbildung und Placentation des Menschen und der Säugetiere, Munich, 1927, J. F. Bergmann, p. 324.
16. Handler, F. P., Blache, J. O., and Blumenthal, H. T.: Arch. Path. **53**: 29, 1952.
17. Hitschmann, J., and Lindenthal, O. T.: Arch. Gynäk. **69**: 587, 1903.
18. Lansing, A. I., Blumenthal, H. T., and Gray, S. H.: J. Gerontol. **3**: 87, 1948.
19. Mandel, H. S., Graff, S., and Graff, A. M.: AM. J. OBST. & GYNEC. **50**: 471, 1945.
20. Novak, E.: Gynecologic and Obstetric Pathology, ed. 3, Philadelphia, 1952, W. B. Saunders Company, p. 541.
21. Probstner, A.: Endokrinologie **8**: 161, 1931.
22. Siddall, R. S., and Hartman, F. W.: AM. J. OBST. & GYNEC. **12**: 683, 1926.
23. Smith, G. van S., and Kennard, J. H.: Proc. Soc. Exper. Biol. & Med. **36**: 508, 1937.
24. Stander, H. J.: Textbook of Obstetrics, New York, 1945, D. Appleton-Century Company, p. 688.
25. Strachan, G. I.: J. Obst. & Gynaec. Brit. Emp. **33**: 262, 1926.
26. Tenney, B., Jr., and Parker, F., Jr.: AM. J. OBST. & GYNEC. **31**: 1024, 1936.
27. Tenney, B., Jr., and Parker, F., Jr.: AM. J. OBST. & GYNEC. **39**: 1000, 1940.
28. Wang, H. S., and Hellman, L. M.: Bull. Johns Hopkins Hosp. **73**: 31, 1943.
29. Williams, J. W.: Am. J. Obst., N. Y. **41**: 775, 1900.
30. Young, J.: J. Obst. & Gynaec. Brit. Emp. **26**: 1, 1914.
31. Young, J.: J. Obst. & Gynaec. Brit. Emp. **34**: 278, 1927.

DIAGNOSIS AND OBSTETRICAL TREATMENT OF HYDROCEPHALUS

A Review of Twenty-nine Births of Hydrocephalic Infants From a Private Hospital

MATTHEW J. BULFIN, M.D., FRANK C. LAWLER, M.D., AND PAUL E. LAWLER, JR., M.D., CHICAGO, ILL.

(From the Department of Obstetrics and Gynecology, Little Company of Mary Hospital, Evergreen Park, Ill.)

THE birth of a hydrocephalic baby is relatively uncommon even in large obstetrical practices. The potential danger to the mother during the labor and delivery is well realized by all. In spite of the widely known hazards of such a complication, there is surprisingly little in recent literature on the management of the delivery of a hydrocephalic baby. We have reviewed all the births of hydrocephalic infants at the Little Company of Mary Hospital during the ten-year period, 1945 through 1954.

Potter and Adair[5] stated:

"In hydrocephalus, there is an increase in size of the head due to enlargement of the individual bones and widening of the sutures. The calvarial bones frequently exhibit irregular fenestrations, and the round or oval defects are covered only by pericranium. Such fenestrations are usually found only in association with increased intracranial pressure. The increase in size of the head is secondary to pressure exerted on bones by overdistention of cerebral ventricles.

"Internal hydrocephalus is characterized by distention of the lateral ventricles of the brain with thinning of the cerebral cortex. The head at birth may be sufficiently enlarged to interfere with delivery or it may be of almost normal size and show no increase until days or weeks later. The enlargement is usually caused by excessive secretion of fluid by choroid plexus or by lack of resorption from subarachnoid space. The failure of resorption may be due to some abnormality of the arachnoid.

"More frequently, the presence of adhesions around the base of the brain prevents outflow of fluid from the ventricular system. In external hydrocephalus an excessive amount of fluid surrounds cerebral hemispheres. This variety is rare in comparison to internal hydrocephalus."

Data on the Series of 29 Births

Incidence.—In a ten-year period from 1945 through 1954 there were 29 hydrocephalic infants in 35,292 deliveries, an incidence of about 1:1,200. Crenshaw and Banner[1] cited the occurrence rate as 1:500, while Feeney and Barry[3] reported the incidence as 2.5 per 1,000. The incidence has been quoted more frequently as about 1:1,000.

There were 16 male infants and 13 females in the series. In a group of 359 children who had been studied as having congenital hydrocephalus at the Mayo Clinic, there were 194 males to 165 females.[1]

There was one set of twins in our series, a male and female, both of whom were hydrocephalic. In the x-ray film taken two weeks before delivery, no diagnosis of hydrocephalus was made in either twin. In three other instances of twin pregnancies with hydrocephalus reported by Crenshaw and Banner, the x-ray taken before delivery also failed to diagnose the anomaly.

None of the mothers in our series had had a previous hydrocephalic infant. One mother, however, had been delivered of an anencephalic infant four years previously. She had one other normal infant.

Prenatal Course.—In our series of cases we were not able to find any one symptom which was universal to all. Polyhydramnios was present in 5 patients. Three had toxemia of pregnancy. Four patients had stated during pregnancy that they felt very little life. Most of the patients presented no outstanding symptom that would be considered characteristic of hydrocephalus in utero. The fetal heart tones as recorded by the attending doctors on the prenatal records exemplified neither bradycardia or tachycardia. Vaginal bleeding during the first trimester occurred in 2 of the 28 patients—not an abnormal finding. Excessive weight gain had occurred in only 5 of the patients.

Maternal Age and Parity.—The average maternal age in our series was 28.5 years. Crenshaw and Banner stated that the common age at which to expect hydrocephalus is in the early thirties. The youngest mother in our 28 cases was a 19-year-old primigravida, while the oldest was a 41-year-old para iii. There were 17 multigravidas and 11 primigravidas. There does not appear to be any correlation in our series between maternal age, parity, and occurrence of hydrocephalic infants.

Diagnosis.—The diagnosis of hydrocephalus was made during prenatal care in 6 of the 28 cases, during labor in 5 cases, and during or after delivery in 17 cases. Of the 11 cases that were diagnosed prior to delivery, careful abdominal and vaginal examinations disclosed the possibility of such a condition, and roentgenographic studies confirmed the diagnosis in each case. However, hydrocephalus of minimal and moderate degrees is a difficult diagnosis to make. In many cases the diagnosis of hydrocephalus cannot be made merely by abdominal palpation. Diagnosis by combined abdominal, vaginal, and radiological examination may even be difficult. Feeney and Barry believed, however, that there are certain signs that should indicate the possibility of hydrocephalus. "The obstetrician should consider the possibility of hydrocephalus when findings on palpation of the fetus do not appear to be quite normal; when the head is not engaged at the onset of labor or when it does not descend during labor in a multipara with a good history; when the lower part of the uterus is tender; when unexpected difficulty arises at any time during labor; when vaginal examination of the fetal head indicates an abnormality—and when the radiologist sounds a warning."

Redman and Airth stated that minor degrees of hydrocephalus should be suspected when there is cephalopelvic disproportion with a very high head that cannot be pushed down despite a normal-sized pelvic brim. When vaginal examination of the fetal head is possible, widely dilated sutures would assure the diagnosis.

An abnormally large fetal head shadow in a roentgenogram, when this has been taken with the patient supine, does not necessarily denote hydrocephalus, but when there is suspicion of it, a lateral pelvimetry film should be made.

Redman and Airth[6] cited the following precautions to be taken during x-ray pelvimetry for hydrocephalus:

1. The fetus must be encouraged to lie still by maternal overbreathing for a minute before the exposure.
2. Cassettes must be changed and the x-ray tube moved to its new position quickly, to shorten the period between exposure.
3. The minimum distance of the x-ray tube from the film should be 30 inches; a lesser distance produces distortion that precludes accurate measurement.
4. The maximum distance should be 50 inches.
5. The source of the x-rays must be centered precisely over the fetal head.

Maternal Mortality.—In a study of 304 births of hydrocephalic infants by Feeney and Barry, there were 9 maternal deaths. Failure of and delay in diagnosis were apparent in all cases.

The one maternal death in our series resulted from failure to diagnose the hydrocephalus during labor. The condition was diagnosed as an arrested transverse presentation. Two attempts were made to effect a forceps rotation after complete dilatation had occurred and the head was at plus 1 station. The patient went into deep shock almost immediately after the operative procedure and died five hours later in spite of eight pints of blood and active supportive measures. A postmortem cesarean section revealed the uterine rupture through the lower segment. An 8 pound hydrocephalic male infant was delivered stillborn.

Length of Gestation.—In 15 of our cases, the patient entered labor at or near term. Seven of the patients were delivered three to six weeks early. Two patients entered labor four weeks beyond due date; one was delivered three weeks late, and 3 two weeks late. In view of the fact that only about 50 per cent of our patients were delivered at or near term, we feel that the mechanism of initiation of labor must be influenced somewhat abnormally when a hydrocephalic fetus is present. As a result of this we are more inclined to use x-ray studies on patients who are two or more weeks overdue or on patients who enter labor prematurely with unsatisfactory progress.

Labor.—The average length of labor in our series for the 11 primigravidas was about 8 hours, and, for the 17 multigravidas, about 11 hours. There were 4 labors in our series over 16 hours in duration and in each of these cases the diagnosis of hydrocephalus was not made until well into labor.

TABLE I. METHODS OF DELIVERY IN 29 BIRTHS OF HYDROCEPHALIC INFANTS

Spontaneous	11
Low forceps and episiotomy	5
Willett scalp traction, episiotomy, and low forceps	2
Breech extraction with episiotomy	8
Version for transverse presentation of dead baby	1
Cesarean section	1
Postmortem cesarean section, uterine rupture	1
Total cases requiring cerebral tap and trocar drainage	7

Table I shows the methods of delivery employed in our series of 29 births of hydrocephalic infants and it is perhaps surprising that such a high percentage of the infants were delivered uneventfully. Only about 9 out of the 29 cases could be considered relatively difficult operative procedures. In the 7 cases that required trocar drainage through the fontanelles, the procedure was done with no untoward effects. In all 7 cases, delivery was effected within four hours of the insertion of the trocar. The only version that was done was

necessary because of a transverse presentation with absent fetal heart tones. The mother entered the hospital in active labor and had not felt life for one week. A submucous fibroid was found to be the cause for the transverse lie. The hydrocephalus was not discovered until after delivery.

The one cesarean section in our series resulted because of a 24 hour labor with x-ray diagnosis of a brow presentation and failure of dilatation beyond 5 cm. Abdominal delivery disclosed the hydrocephalus. The head was 40 cm. in circumference and yet the x-ray in this instance failed to reveal the condition.

The Infant.—The average weight of the infant in our series was 6 pounds, 11 ounces, with weights ranging from 5 pounds, 1 ounce, to 9 pounds.

TABLE II. PROGNOSIS FOR THE HYDROCEPHALIC INFANT

Stillbirths	12	
Born alive	17	
Lived 24 hours or less		9
Lived one month or less		6
Lived 33 days		1
Lived 94 days		1

Of the 29 infants in our series, 17 were born alive and 12 were stillborn (Table II). Of those stillborn, death occurred prior to labor in 8 cases and during labor in 4 cases. Of the 17 infants who were born alive, 3 died within one hour, 6 died within 24 hours, 6 died within one month, and 2 lived 33 days and 94 days, respectively.

Hydrocephalus was accompanied by spina bifida in 10 of the 29 infants. Three infants also had clubfeet. In one case, hydrocephalus was of such mild degree at birth that it was not noticed until the attending pediatrician diagnosed the condition three days after birth.

Postpartum Course.—The postpartum course of 23 of the 28 mothers was uneventful. Three had had moderately severe toxemia during the last weeks of pregnancy and as a result were hospitalized longer post partum. One patient ran a temperature of 101° to 104° F. recurrently for eleven days post partum. This was attributed to endometritis. The one maternal death occurred five hours post partum from a ruptured uterus.

Management of Hydrocephalus

If the diagnosis of hydrocephalus is made prior to labor or during the latter part of pregnancy, the condition should be made known to both husband and wife. The treatment at this time is mostly of a psychic nature; the patient should have her fears allayed as much as possible. The important aspect of treatment at this stage is to keep the patient as comfortable as possible. The possibility of a normal delivery can be mentioned for it is true that some hydrocephalic infants can be delivered with surprisingly little trauma, especially in multiparas. The possibility of a mutilating, destructive type of procedure should not be dwelt upon with either the husband or the patient. Certainly, the delivery of hydrocephalic infants is much less a traumatic procedure today than in years previously. One of the patients in our series was a former Army nurse in whom the diagnosis of hydrocephalus was established at seven and one-half months because of a huge polyhydramnios and grossly enlarged head that was palpated upon abdominal examination. The condition was made

known to both her and her husband. Their questions were answered in as reassuring a manner as possible, and the patient made an excellent adjustment to the situation. Delivery at term was uneventful after drainage of 1,100 c.c. of fluid by trocar through the anterior fontanelle.

In the event that the hydrocephalus is not diagnosed until after the onset of labor, further trial labor should be allowed until the extent of the disproportion can be evaluated. Occasionally these patients will be delivered without operative interference. If a definitely obstructed labor ensues, trocar drainage through the anterior fontanelle should be done. This can be accomplished readily with as little as 3 cm. dilatation of the cervix. In most cases, labor will progress quickly thereafter.

In the event of breech presentation with hydrocephalus and spina bifida, a metallic or stiff silk catheter may be passed through a defect in the vertebral arches in a manner described by Plass.[4]

Fara, Foss, and Philipp[2] describe a method of transabdominal paracentesis that was used successfully at the Cook County Hospital for management of hydrocephalus with breech presentation: "A 15 gauge spinal needle with the stylet in place was introduced through the anterior abdominal wall until resistance was encountered at a distance of about 4 cm. Slight additional pressure was sufficient to penetrate the fetal skull and enter the cranial vault. The stylet was removed and clear cerebrospinal fluid was obtained under pressure. The head was allowed to decompress slowly." Labor followed shortly afterward and the patient delivered a full-term hydrocephalic infant spontaneously from the right sacral posterior position.

As in so many matters that touch upon survival or death, ethical considerations enter here. It is recognized that, in various moral problems, there is sometimes found among physicians a divergence of opinion. Accordingly, we will set down the moral views by which we are guided in the management of hydrocephalus.

Craniotomy is never employed as we regard it as a direct destruction of an individual life. This explains the absence of such an approach in any case in our series, even though such an operation might be operatively quite possible. We regard the drainage of fluid from the brain by means of trocar or cannula insertion as ethical because the operation is not done with a view to the destruction of the child. The same considerations govern here that are properly used to justify other delicate surgery. This procedure is not necessarily synonymous with destruction of the fetus and cannot be described as an attack on the fetus any more than an urgent cerebral operation on an adult is an attack upon him, even if death does unhappily follow.

From the practical point of view, this abstinence from craniotomy avoids the possibility of destruction of an infant that might conceivably have had an erroneous diagnosis of hydrocephalus. Certainly, this possibility, although most unlikely, should nevertheless be considered.

Summary and Conclusions

1. We have reviewed 29 births of hydrocephalic infants that occurred during the years 1945 through 1954. There were 35,292 deliveries during this period, giving an incidence of 1:1,200.

2. We found in this group of mothers no history of previous infants with hydrocephalus or with an undue number of congenital malformations.

3. The diagnosis of hydrocephalus was made in only 11 of our 29 cases prior to delivery. In 5 cases in which x-rays were taken, the diagnosis still was not made.

4. There was no predominant symptom that was universal in all cases. Polyhydramnios occurred in only 5 cases. The amount of fetal movement and fetal tachycardia or bradycardia were not remarkable.

5. The average maternal age was 28.5 years.

6. Only 50 per cent of our patients were delivered at or near term. As a result we believe that it is well to keep hydrocephalus in mind when a patient is two or three weeks past term or enters labor prematurely with failure of normal progress.

7. Meticulous x-ray technique is necessary if all cases of hydrocephalus are to be confirmed by this means. The diagnosis of hydrocephalus in twins and breech births is especially difficult.

8. We do not employ craniotomy for the ethical reasons stated. Trocar drainage of the fontanelles or insertion of a catheter through the spinal canal offers more satisfactory methods of management. Anesthesia is ordinarily not necessary for this procedure.

9. We have been strongly impressed with the importance of early recognition of the hydrocephalus. The overdistention and thinning out of the lower uterine segment from this unrecognized obstructive mechanism carries with it the definite hazard of rupture of the uterus. If every doctor who does obstetrics could train himself to consider the possibility of hydrocephalus in any case of obstructed labor, the incidence of maternal mortality throughout the country would undoubtedly show a further decrease toward the long-sought-after irreducible minimum.

References

1. Crenshaw, J. L., and Banner, E. A.: Am. J. Obst. & Gynec. **63**: 63, 1952.
2. Fara, F. J., Foss, H. G., and Philipp, E. A.: Am. J. Obst. & Gynec. **67**: 158, 1954.
3. Feeney, J. K., and Barry, A. P.: J. Obst. & Gynaec. Brit. Emp. **61**: 652, 1954.
4. Plass, E. D.: Am. J. Obst. & Gynec. **55**: 548, 1948. (Correspondence.)
5. Potter, Edith L., and Adair, Fred L.: Fetal and Neonatal Death, ed. 2, Chicago, 1949, The University of Chicago Press.
6. Redman, T. F., and Airth, G. R.: J. Obst. & Gynaec. Brit. Emp. **60**: 888, 1953.

1150 West 78th Street.

A CRITICAL EVALUATION OF BIOLOGICAL PREGNANCY TESTS

ROSE L. BERMAN, B.A., NEW YORK, N. Y.

(From the Berman Clinical Laboratory)

FOR a number of years, confusion and error have resulted from reliance upon various pregnancy tests which too often yield false positive and/or false negative reactions. Mice, rats, rabbits, frogs, and toads have been employed as test animals, in many instances, with indifference to the conditions that usually vitiate the test. In some cases, although the test may be considered sufficiently accurate by some, its value for routine use is limited by important and unavoidable factors. The purpose of this paper is to set forth some of the important causes of confusion and error that exist concerning pregnancy tests. The pregnancy tests to be discussed are the Aschheim-Zondek (mouse), Friedman-Lapham (rabbit), female and male frog (toad) tests, and the Frank-Berman (rat) test and proposed modifications of this test, with detailed emphasis on the frog-toad and rat tests which are commonly employed today.

Aschheim-Zondek Test.—This test was discovered by Selmar Aschheim in 1927[1-4] and was published by Aschheim and Zondek[5] in 1928. In this test 5 immature (5 to 7 gram) female mice are injected subcutaneously with varying doses of urine. The animals are given 6 injections over a period of 2 days, the total amount of urine injected varying from 1.2 to 2.4 ml. The end point of reaction is the formation of corpora lutea. The results, which are obtained 100 hours after the first injection is administered, are accurate up to about 97-98 per cent.

Serious objections to the employment of this test are as follows: (a) a substantial number of animals are killed by the injection of the test urine[7]; (b) in about 12 per cent of tests, section and microscopic examination of the test ovaries are required since the result cannot be satisfactorily seen with the naked eye[9]; (c) the test requires a lengthy period (100 hours) for satisfactory results; (d) because of the time element and work schedules the test can be started only on Mondays, Tuesdays, and Thursdays[6] thus delaying the rendering of a result well beyond the 100 hours required for the test itself.

Friedman-Lapham Test.—This test was discovered by Maurice H. Friedman and Maxwell E. Lapham[8, 9] in 1931. It is a decided improvement over the Aschheim-Zondek test in that results are available in 48 hours without sacrificing accuracy. This test is performed on female rabbits which receive 3 intravenous injections of urine daily for 2 days and are sacrificed on the third day. The end point of reaction is the formation of fresh corpora lutea or large bulging corpora hemorrhagica. The principal objection to this test is the indispensability of isolating the rabbits in solitary confinement for a period of 30 days before use. This precaution is necessary to avoid the complication of ovulation in the test animals. Its proper use, therefore, is limited to institutions where large animal quarters are available.

Frog (Toad) Tests.—

A. Female species: Bellerby[10] and Shapiro and Zwarenstein[11, 12] in 1934 described a test in which the female South African clawed toad *(Xenopus laevis)*

TABLE I. TOAD (FEMALE) PREGNANCY TEST FINDINGS

REFERENCE	TOTAL NO. TESTS	NO. POSITIVES	NO. CORRECT POSITIVES	NO. FALSE NEGATIVES	% INACCURACY	NO. NEGATIVES	NO. CORRECT NEGATIVES	NO. FALSE POSITIVES	% INACCURACY
Weisman and Coates[13]	1,000	684	673	11	1.6	316	316	0	0
Landgrebe and Samson[14]	220 cases with 2 false negatives								
von Wattenwyl[15]	182	84	75	9	10.7	98	98	0	0
Oliver and Miller[16]	354	159	156	3	1.9	195	195	0	0
Rasmussen[17]	87	69	57	12	17.4	18	18	0	0
Sanders[18]	150	?	?	2	?	?	?	0	0
Robbins et al.[19]	100	49	45	4	8.2	51	51	0	0
Foote and Jones[20]	142	67	46	14	20.9	75	75	0	0
Landgrebe and Hobson[21]	?	98-99% accurate with false positives and false negatives							
Dittebrandt[23]	533*	?	?	12	?	?	?	0	0
	567*	?	?	7	?	?	?	0	0
Langford[24]	154	89	81	8	9.0	73	73	0	0
Spurny and Hess[25]	?	82% accuracy							
Marsters et al.[26]	400	170	146	24	14.1	230	228	2	0.9
Hobson[27]	37,020†	?	?	(0.2%)	?	?	?	0	0
Freytag et al.[28]	260	136	112	24	17.6	124	116	24	8.0
Benitez et al.[29]	122 (Using serum)	?	?	8	?	?	?	0	0

*Utilizing 2 different extraction methods.
†Claims 99.8 per cent accuracy.

is employed. The urine to be tested is first precipitated and then extracted. The extract obtained is injected into 6 toads and the end point of reaction is indicated by extrusion of macroscopic ova through the cloaca. Ovulation occurs in about 5 to 24 hours. If after 24 hours no ovulation has occurred, the animals are sacrificed and postmortem is performed to search for retained ova. The authors found that about 7 per cent of positive reactions were oviducal positives. If a negative result is obtained the test must be repeated 10 to 14 days later on 6 more animals with a second specimen of urine collected by the patient. In spite of this, they[12] reported on 441 cases—306 pregnancy cases, of which 296 gave correct positives and 10 gave incorrect negatives (3.3 per cent inaccuracy), and 135 tests were correct negatives. The authors advise that during the breeding season (July to September in South Africa), it is necessary to isolate the test animals for at least one week and controls should be killed and examined. They also advise that if toads are kept in the laboratory longer than 3 to 4 weeks, they become insensitive to the injections of extracted urine and incorrect negatives may be obtained. The findings of other investigators are summarized in Table I, with the per cent inaccuracy in positive and negative tests noted.

Foote and Jones[20] report that normal intrauterine pregnancy cannot be diagnosed before the fortieth day of gestation and that following this period the expected accuracy is 95-96 per cent with no false positives. Schwabacher[22] found that some toads failed to ovulate until 48 hours after injection.

The value of this test is limited by the following factors: (a) precipitation and extraction of the urine specimen to be tested are necessary, a long and tedious process, and accuracy of results therefore may vary in different hands; (b) patients on whom negative results are obtained must report back in 10 to 14 days for retest because of the high percentage of false negatives; (c) in spite of retest, false negative results may be expected; (d) every investigator, including the discoverers, has reported false negative results and a few have reported false positive results; (e) special handling of test animals is required during the summer months.

B. Male species (toad and frog): Galli Mainini[30, 31] in 1947 proposed the use of the South American male toad *(Bufo arenarum Hensel)* for pregnancy testing. The reaction elicited in the toad is the ejaculation of spermatozoa a few hours after injection of test urine from a pregnant woman. Galli Mainini's accuracy based on 99 cases was 94-95 per cent with both false positive and false negative results obtained. He expressed doubt as to the use of the male toad as a test animal for pregnancy because of the lessened reactivity of the toads during various seasons of the year, during the mating period or variations of temperature. In 1948, in a review paper, he[32] reported on 1,422 cases with accuracy figures ranging from 98-100 per cent. He also reported that Pinto and Suer Boero[33] obtained negative results in one case of chorionepithelioma (a condition in which a large excess of chorionic gonadotropin exists).

Wiltberger and Miller[34, 35] in 1948 published reports on the use of the North American (frog) *Rana pipiens* for pregnancy testing. They reported that in the first trimester of pregnancy they obtained 100 per cent accurate results. With specimens from the last trimester of pregnancy, however, their accuracy figure was reduced to 50 per cent. By 1950, reports from this group[36] were beginning to change. They reported many false negative results with the use of *Rana pipiens* and proposed various changes in the technique of the test. They suggested the use of another species of frog, *Rana clamitans,* during the month of August. They also recommended concentrating and extracting the urine specimen to be tested, storage of frogs in shallow water and in a refrigerator, the temperature at which to run tests, etc.

TABLE II. FROG-TOAD (MALE) PREGNANCY TEST FINDINGS

REFERENCE	TOTAL NO. TESTS	NO. POSITIVES	NO. CORRECT POSITIVES	NO. FALSE NEGATIVES	% INACCURACY	NO. NEGATIVES	NO. CORRECT NEGATIVES	NO. FALSE POSITIVES	% INACCURACY
Pigeaud et al.[83]	335	335	320	15	4.5	–	–		
Bedoya and Puros[84]	184	107	107	0	0	77	77	0	0
Wagner and Shanahan[85]	101	57	55	2	3.6	44	44	0	0
Goldzieher et al.[86]	310	147	124	24	16.5	163	155	8	4.9
Haskins and Sherman[87]	800	406	388	18	4.4	394	389	5	1.3
Reinhart et al.[88]	471	346	343	3	0.9	125	125	0	0
Holyoke and Hoag[89]	211	113	93	17	17.7	98	98	0	0
Lambeth[90]	100	77	68	9	11.7	23	23	0	0
Laubmann[91]	95	48	44	4	8.3	47	45	2	4.3
Thorborg[92]	1,025	568	551	17	3.0	457	457	0	0
Klahn[93]	100	52	51	1	1.9	48	48	0	0
Dornes and Saclisse[94]		95 tests with 1 false negative							
Bromberg et al.[95]		700 cases—diagnosis possible in only 598 cases (accuracy 85%)							
Forman and Floyd[96]	278	173	168	5	2.9	95	95	0	0
Hause[97]	107	23	8	15	65.2	84	78	6	7.1
Mukherjee[98]	196	145	141	4	2.8	51	50	1	1.8
Frusch[99]	317	179	177	2	1.1	138	127	11	8.0
Farrant and Buckland[100]	66	32	28	4	12.5	34	34	0	0
Schüller[101]	429	187	187	0	0	236	233	3	1.3
Lambeth[102]	100	77	68	9	11.8	23	23	0	0
O'Hanrahan[103]	229	115	107	8	7.0	114	109	5	4.4
Hodgson[104]	203	180	157	23	14.6	147	137	10	7.2
	100	54	53	1	1.9	46	45	1	2.2
Freytag et al.[28]	469	279	243	36	12.5	169	148	21	12.4

Casas et al.[40]	150	99	88	11	11.1	50	50	0	0
Sandoval[41]	100	65	60	5	7.7	30	30	0	0
Haines[42]	50	?	(No false positive—1 false negative)						
Haines[43]	100	?	(4 false negatives)						
Castillo[44]	102	62	60	2	3.2	43	40	3	7.0
Heredia[45]	238	225	216	9	4.0	13	13	0	0
Sandoval[46]	100	70	65	5	7.2	30	30	0	0
Manstein and Schmidt-Hoensdorf[47]	123	69	69	0	0	54	54	0	0
Herrera et al.[48]	467	202	202	0	0	265	265	0	0
D'Arcy and Grönwall[49]	100	56	56	0	0	44	44	0	0
Vasconcelos and Leas[50]	403	244	242	2	0.8	159	158	1	0.6
Sulman and Sulman[51]	500	(Accuracy 85%—77 false negatives and false positives)							
Brody[52]	111	66	55	11	16.7	48	48	0	0
Klopper and Frank[53]	101	59	51	8	15.7	42	42	0	0
Mello[54]	175	?	(5 false negatives)						
de Aquino Salles et al.[55]	1,180	707	689	18	2.5	473	473	0	0
Bhaduri and Barahan[56]	110	58	58	0	0	52	52	0	0
McCallin and Whitehead[57]	140	67	65	2	3.0	73	73	0	0
D'Arcy[58]	260	?		7		?	?		
Soucy[59]		(70% accuracy on tests done July-September 15)							
Gardner and Harris[60]	23	23	20	3	13.0	(5-8 weeks' amenorrhea)			
	33	33	30	3	9.1	(8-12 weeks' amenorrhea)			
	41	41	27	14	34.1	(12-16 weeks' amenorrhea)			
	62	62	22	40	64.4	(16-20 weeks' amenorrhea)			

TABLE II—CONT'D

REFERENCE	TOTAL NO. TESTS	NO. POSITIVES	NO. CORRECT POSITIVES	NO. FALSE NEGATIVES	% INACCURACY	NO. NEGATIVES	NO. CORRECT NEGATIVES	NO. FALSE POSITIVES	% INACCURACY
Bell et al.[61]	343	198	177	21	10.6	145	145	0	0
Bieniarz[62]	156	?		15	?	?		0	0
Bettinger and O'Loughlin[63]	148	57	50	7	12.3	98	98	0	0
Bivens[64]	203	146	144	2	1.4	57	57	0	0
McCarthy and Soucy[65]	384	237	231	6	2.6	147	147	0	0
Sulman and Sulman[66]	306	143	118	25	17.5	163	158	5	3.0
Sharnoff and Zaino[67]	47	23	14	9	39.2	24	24	0	0
Jones and Jones[68]	127	53	52	1	1.9	74	74	0	0
McCallin and Whitehead[69]	163	79	77	2	2.5	84	84	0	0
Chu[70]	122	97	92	5	5.2	25	25	0	0
Waldrop and James[71]	100	62	50	12	19.3	38	36	2	5.6
Frazer and Wohlzogen[72]	80	54	53	1	1.9	26	26	0	0
Greenblatt et al.[73]	323	?	?	6	?	?	?	2	?
Johnson[74]	235	138	136	2	1.5	97	97	0	0
Spurny and Hess[25]	224	107	105	2	1.9	117	117	0	0
Brede[75]	76	30	29	1	3.3	46	46	0	0
Earle[76]	850	450	409	41	9.1	400	400	0	0
Felding[77]	162	75	53	22	29.3	87	85	2	2.3
Szejnberg and Rabau[78]	109	54	54	0	0	55	55	0	0
de Moraes[79]	200	150	148	2	1.3	50	50	0	0
Brazel[80]	162	79	79	0	0	83	83	0	0
Parmentier[81]	100	50	50	0	0	50	50	0	0
Beckenback and Paul[82]	244	132	125	7	5.3	112	112	0	0

Almost simultaneously in 1948, Robbins and Parker[37] also published a paper on the use of *Rana pipiens* for pregnancy tests. Their experiments were carried out in the winter months. Nevertheless, in 78 cases of pregnancy, they obtained one false negative result (1.3 per cent inaccuracy) in a patient 4 weeks pregnant. Forty-four negative results were all correct negatives. In 1949 they[38] reported on 242 additional tests with the following results: 124 pregnancy cases with 113 correct results and 11 with false negative results (9 per cent inaccuracy) and 118 negative cases with 117 correct negatives and 1 false positive (0.8 per cent inaccuracy).

From this series they excluded all cases which gave them false negative results in patients with amenorrhea of less than 15 days. If these cases had been included we can readily see that the inaccuracy percentage would be higher than 9 per cent in pregnancy cases. Since their paper was submitted, they changed their procedure from that of using a dosage of 5.0 ml. of untreated urine to 20.0 ml. of precipitated and extracted urine. In 1951 a report[39] was made on 404 tests using the 20.0 ml. dose of extracted urine with the following results: out of 118 pregnancies, 110 were correct positives and 8 were false negatives (6.8 per cent inaccuracy) and 286 correct negatives.

It is interesting to note that it was also reported that an occasional false positive occurs with urine from women throughout the menstrual cycle and from menopausal urine. They state: "All attempts at elucidating these reactions have failed, except that the substance causing them does not appear to be of ovarian origin or to be gonadotropin." Therefore with urine specimens from patients who do not have amenorrhea or from menopausal women, they employ rats or rabbits to perform pregnancy tests. It is also noted that in March, April, and May (the mating season), the "spermatic ejaculatory response appears to be highly unstable and somewhat nonspecific" since spontaneous ejaculation occurs after simple handling. All frogs must be examined before use.

Since the appearance of these papers, reports have appeared concerning the use of many species of Bufo (toad) and Rana (frog). Findings are summarized in Table II, with the per cent of inaccuracy in positive and negative tests noted.

There are many serious objections to the use of the male frog or toad as a test animal for pregnancy. The objections are: (a) spontaneous ejaculation of spermatozoa is known to occur; (b) ejaculation of spermatozoa can also be induced with distilled water, follicle-stimulating hormone, Gonadophysin, Polyansyn, etc.[105, 106]; (c) false negatives occur whether untreated urine, extracted urine, or serum is used; (d) false positives occur in spite of all precautions; (e) seasonal variations occur during the summer months, running from April through September, making them very unreliable test animals; (f) because of variations of temperature in various parts of the world and because of unseasonal heat waves occurring at varying times, how is one to determine the time of "seasonal unreliability"? (g) rejection of urine specimens from menopausal patients because of false positive results obtained requires taking a history of each patient to decide which pregnancy test to supply, a most impractical procedure for a well-organized laboratory; (h) false positive results have been reported with urine from jaundiced patients[107]; (i) extraction and precipitation methods preparing urine for injection are cumbersome and time consuming.

Many investigators[53, 105, 106, 112, 113] have referred to the work of Rugh[108-111] as a foundation for the use of male frogs in pregnancy testing. Dr. Rugh, my former Professor, who has spent many years directing research in experimental embryology, has this to say[114]: "Many years ago I used frogs, toads and

TABLE III. RAT HYPEREMIA

YEAR	HOURS OF SACRIFICING RATS	REFERENCE	ML. URINE INJECTED	ROUTE OF INJECTION*	NUMBER RATS	WEIGHT OF RATS (GRAMS)
1944	24	Ramsey et al.[118]	6.0	S.C.	1	35-40
1944	24	Soman[119]	3.0	S.C.	2	30-65
1945	24	Zondek et al.[120]	4.0	S.C.	2	20-25
1947	24	Fried[121]	2.0	I.P.	1	30-60
1948	24	Behnken et al.[122]	5.0	S.C.	2	30-60
1949	24	Riddell[123]	4.0	S.C.	1	30-50
1949	24	von Massenbach[124]	4.0	S.C.	2	20-25
1950	24	Farris[125]	2.0	S.C.	2	30-50
1952	16	O'Hanrahan[103]	1.5	I.P.		
1943	8	de Aquino Salles[126]	10.0	S.C.	2	50
1945	8	Amoral[127]	10.0	S.C.	3	40-50
1942	6	Salmon et al.[128]	2.0	S.C.	3	35-45
1943	6	Kupperman et al.[129]	5.0	S.C.	1	Adult—any weight
1944	6	Kaminester[130]	2.0	S.C.	2	30
1944	6	Kline[131]	2.0-5.5	S.C.	2	35-55
1944	6	Ramsey et al.[118]	4.0	S.C.	1	35-40
1945	6	Zondek et al.[120]	4.0	S.C.		20-25
1946	6	Kupperman and Greenblatt[132]	2.5	S.C.	2	30-80
1946	6	Soman[133]	4.0	S.C.	1	35-45
1947	6	Bunde[134]	2.0	S.C.	1	Immature
1947	6	Fried[121]	2.0	I.P.	1	30-60
1948	4-6	Riley et al.[135]	2.0	I.P.		35-75
1948	6	Kelsey et al.[136]	2.0	S.C.	3	35-55
1949	6	von Massenbach[124]	4.0	S.C.		
1949	6	de Aquino Salles[126]	4	S.C.		
1951	6	Hoffman et al.[137]	4.0	S.C.	2	21-26 days
1952	6	O'Hanrahan[103]	1.5	I.P.		
1944	4	Ramsey et al.[118]	4.0	S.C.		
1949	4	Albert[138]	2.0	S.C.	3-5	35-50
1951	4	Hoffman and Giordano[137]	2.0 2.0	S.C. I.P†	2	26-32
1949	3	Fried[139]	2.0	I.P.	2	30-60
1950	3	Fried and Rakoff[140]	2.0 2.0	I.P. I.P.	2 1	45-60 45-60
1943	2	Kupperman et al.[129]	1.5	I.P.	2	30-100
1944	2	Ramsey et al.[118]	4.0	S.C.		
1944	2	Farris[141]	2.0	S.C.	2	30-45
1945	2	Zondek et al.[120]	4.0	S.C.	2	20-25

*S.C., Subcutaneous.
I.P., Intraperitoneal.
I.V., Intravenous.
†Pituitary synergist.

PREGNANCY TEST FINDINGS

NO. POSITIVES	NO. CORRECT POSITIVES	NO. FALSE NEGATIVES	% INACCURACY	NO. NEGATIVES	NO. CORRECT NEGATIVES	NO. FALSE POSITIVES	% INACCURACY
	(100% accurate)						
	(100 tests with 5 false negatives)						
128	128	0	0	172	169	3	1.2
	(2 false negatives in 8 cases)						
311	306	5	1.6	278	277	1	0.4
62	62	0	0	38	36	2	5.3
27	25	2	3.7	38	38	0	0
42	?	?	(Claims to be able to predict abortion)				
156	150	6	3.8	134	129	5	3.7
25	25	0	0	25	24	1	4.0
40	37	3	7.5	26	26	0	0
78	77	1	1.3	31	31	0	0
48	46	2	4.2	38	38	0	0
62	61	1	1.6	44	43	1	2.3
101	91	10	9.9	82	82	0	0
	(96.5% accurate)						
128	117	11	8.0	172	172	0	0
252	252	0	0	239	239	0	0
	(100 tests, 1 false negative, 3 indefinite readings)						
72	43	29	40.3	8	8	0	0
	(3 false negatives in 39 cases)						
128	126	2	1.6	66	64	2	2.9
496	488	8	1.6	546	543	3	0.5
25	22	3	12.0	32	32	0	0
	? (5-20% false negatives)						
	(83% accuracy in 300 tests)						
46	46	0	0	34	34	0	0
	(Says unreliable—gives no figures)						
	(970 Cases—No details given except 7 false negatives)						
	(80% accuracy in 50 tests)						
	(68% accuracy with 12% false positives)						
114	101	13	11.4	85	84	1	1.2
99	88	11	11.1	101	101	0	0
95	94	1	1.1	103	103	0	0
48	46	2	4.2	38	38	0	0
	(Unreliable)						
98	52	46	46.9	30	15	15	50.0
128	88	40	31.3	172	172	0	0

TABLE III—

YEAR	HOURS OF SACRIFICING RATS	REFERENCE	ML. URINE INJECTED	ROUTE OF INJECTION*	NUMBER RATS	WEIGHT OF RATS (GRAMS)
1946	2	Kupperman and Greenblatt[132]	2.0	I.P.	2	30-80
1947	2	Bunde[134]	1.5	I.P.	1	Immature
1947	2	Fried[121]	2.0	I.P.	1	30-60
1947	2	Kupperman and Greenblatt[142]	2.0-2.5	I.P.		30-80
1948	2	Fried[143]	2.0	I.P.		30-60
1949	2	Fried[144]	2.0	I.P.	3	
1950	2	Greenblatt et al.[73]	2.0	I.P.	2	30-75
1949	2	de Aquino Salles et al.[55]	2.0	I.P.		
1949	2	von Massenbach[124]	2.0	I.P.		
1952	1½	Hofman[145]	2.0	I.P.	2	
1949	1	Fried and Rakoff[146]	2.0	I.P.	2	45-60
			2.0	I.P.†	2	45-60
1951	1	Sturgis and Haour[147]	2.0	I.V.		

salamanders in the hope of finding a reliable test animal for pregnancy. It is true that salamanders and toads will often respond to the extract of mammalian pituitary known as Antuitrin-S, but frogs are entirely refractile. Pregnancy urines will occasionally elicit response by ovulation or ejaculation of sperm in the toad Xenopus, but the response is so dependent upon the physiological condition of the test animal that the results are unreliable. So far as frogs are concerned, any excitation of the male frog, particularly as the normal breeding season approaches, will cause the liberation of sperm. The disparity between the human (mammal) and the cold-blooded amphibia (frogs, toads, etc.) is so great in every respect that it is doubtful that the influence of foreign toxins can be so controlled as to provide a reliable test for pregnancy alone. While I am prejudiced toward the amphibia, from long experience with them, I would never rely upon any of them for a valid test of human pregnancy."

Frank-Berman Test.—A series of experiments in 1940-1941 established that the immature female rat can be employed as a completely reliable test animal for pregnancy diagnosis. This test was described by Frank and Berman[115] in 1941 with results obtainable within 8 to 24 hours. Results were found to be 100 per cent reliable if read in 16 to 24 hours. It is an extremely simple test involving the subcutaneous injections of two 5.0 ml. quantities of centrifuged, untreated urine into each of 2 immature 50 gram female rats and sacrifice of the animals with illuminating gas the following morning (16 to 24 hours after the first injection). The rats' ovaries are examined grossly with the naked eye. Pregnancy urine produces a characteristic hyperemia of the ovaries. Details and full discussion of the test as well as indispensable precautions have been published recently.[116] This was the first successful pregnancy test using rats with results obtained within 8 to 24 hours and in my hands has yielded completely accurate results in the 16 to 24 hour period in over 9,000 tests. The test utilizes untreated, centrifuged urine or blood serum and is inexpensive and simple to read.

The published results made it clear that the 8 hour reaction is reliable only if the result is positive. A negative test result cannot be relied upon unless con-

CONT'D

NO. POSITIVES	NO. CORRECT POSITIVES	NO. FALSE NEGATIVES	% INACCURACY	NO. NEGATIVES	NO. CORRECT NEGATIVES	NO. FALSE POSITIVES	% INACCURACY
367	363	4	1.1	385	385	0	0
72	41	31	43.1	8	8	0	0
111	107	4	3.6	78	78	0	0
604	599	5	0.8	602	601	1	0.2
275	263	12	4.4	245	242	3	1.2
122	107	15	12.3	78	78	0	0
	(7 false positives in 300 patients)						
	(3-10% false negatives)						
21	14	7	33.3	33	32	1?	3.0
	(10 false positives in 100 cases)						
63	52	11	17.6	30	30	0	0
114	110	4	3.5	49	49	0	0
103	96	7	6.8	219	219	0	0

firmed by the 16 to 24 hour test. In the original studies all dose ranges of urine were tested, untreated and extracted urines were used, and animals were sacrified at different time intervals, intravenous (tail vein), intraperitoneal, as well as subcutaneous injections were tried, and rats of various sizes were used. We were able to obtain results in as short a time as one-half hour after injecting the rats. In answer to a query from Zondek, we[117] reported in 1942: "Even in four hours, positive reactions have been obtained but further study will be necessary before the reliability of these shorter observations will be considered trustworthy." Because we obtained so many false negative results with known pregnancy urines, we dropped further work and did not deem these results worthy of publication.

The findings of other investigators who have modified the Frank-Berman technique are presented in Table III with the per cent of inaccuracy noted.

It will be noted that the modifications of the Frank-Berman technique are: (a) in dosage of urine used, 1.5 to 6.0 ml. instead of 10.0 ml.; (b) in number of rats used per test, 1 to 5, instead of 2; (c) in injection route, intravenous and intraperitoneal, instead of subcutaneous; (d) in weight of rats used, 20 grams to adults, instead of 50 grams; (e) in time of sacrificing animals, 1, 2, 3, 4, 6, 8, 16, and 24 hours, instead of 16 to 24 hours. The inaccuracy figures for the various modifications have been reported up to 46.9 per cent in pregnancy cases and up to 50 per cent in nongravid cases, in contradistinction to 100 per cent accuracy obtained by Frank and Berman.

It is apparent that the shorter the time interval between injection of the specimen and sacrifice of the rats and the smaller the dose of urine used, the greater will be the percentage of inaccurate results obtained. None of the proposed modifications have improved upon the Frank-Berman test.

Summary

1. The literature on biological pregnancy tests since 1928 has been reviewed.

2. The Aschheim-Zondek (mouse) and Friedman-Lapham (rabbit) tests are briefly discussed.

3. Male and female frog-toad tests, and the Frank-Berman (rat) test and its proposed modifications are more fully reviewed.

Bibliography

1. Aschheim, S.: Ztschr. f. arztl. Fortbild. **26**: 5, 1929.
2. Aschheim, S.: Rev. méd. german.-ibero-am. **2**: 622, 1929.
3. Aschheim, S.: Abhandl. Geburtsh. u. Gynäk. **3**: 6, 1930.
4. Aschheim, S.: J. Lab. & Clin. Med. **27**: 547, 1942.
5. Aschheim, S., and Zondek, B.: Klin. Wchnschr. **6**: 1404, 1928.
6. Aschheim, S.: Am. J. Obst. & Gynec. **19**: 335, 1930.
7. Frank, R. T.: The Female Sex Hormone, Springfield, Ill., 1929, Charles C Thomas, publisher.
8. Friedman, M. H.: Am. J. Physiol. **90**: 617, 1929.
9. Friedman, M. H., and Lapham, M. E.: Am. J. Obst. & Gynec. **21**: 405, 1931.
10. Bellerby, C. W.: Nature **133**: 494, 1934.
11. Shapiro, H. A., and Zwarenstein, H.: Nature **133**: 762, 1934.
12. Shapiro, H. A., and Duncan, D. G.: Clin. Proc. **3**: 186, 1944.
13. Weisman, A. I., and Coates, C.: West. J. Surg. **52**: 171, 1944.
14. Landgrebe, F. W., and Samson, L.: J. Obst. & Gynaec. Brit. Emp. **51**: 133, 1944.
15. von Wattenwyl, H.: Gynaecologia **121**: 29, 1946.
16. Oliver, J. A., and Miller, M. F.: Arizona Med. **3**: 31, 1946.
17. Rasmussen, R. F.: Am. J. Clin. Path., Tech. Sect. **10**: 15, 1946.
18. Sanders, C. B.: Texas J. Med. **42**: 375, 1946.
19. Robbins, S. L., Parker, F., and Doyle, W. C.: New England J. Med. **234**: 784, 1946.
20. Foote, E. C., and Jones, G. E. Seegar: Am. J. Obst. & Gynec. **51**: 672, 1946.
21. Landgrebe, F. W., and Hobson, B. M.: Brit. M. J. **2**: 17, 1949.
22. Schwabacher, H.: Brit. M. J. **2**: 328, 1950.
23. Dittebrandt, M.: Am. J. Clin. Path. **19**: 284, 1949.
24. Langford, C. L.: New Orleans M. & S. J. **102**: 453, 1950.
25. Spurny, J., and Hess, C.: Wien. klin. Wchnschr. **62**: 137, 1950.
26. Marsters, R. W., Black, M. E., and Randall, J. D.: Am. J. Obst. & Gynec. **60**: 752, 1950.
27. Hobson, B. M.: J. Obst. & Gynaec. Brit. Emp. **59**: 352, 1952.
28. Freytag, R. E., Hullinghorst, R. L., Hunter, G. W., and Ritchie, L. S.: J. Lab. & Clin. Med. **42**: 646, 1953.
29. Benitez, R. E., Phillips, G. W., and Kulns, D. M.: U. S. Armed Forces M. J. **5**: 815, 1954.
30. Galli Mainini, C.: Semana méd. **1**: 337, 1947.
31. Galli Mainini, C.: Endocrinology **7**: 653, 1947.
32. Galli Mainini, C.: J. A. M. A. **138**: 121, 1948.
33. Pinto, M., and Suer Boero, H.: Obst. y. ginec. latino.-am. p. 556, 1947.
34. Wiltberger, P. B., and Miller, D. F.: Science **107**: 98, 1948.
35. Miller, D. F., and Wiltberger, P. B.: Ohio J. Science **48**: 89, 1948.
36. Giltz, M. F., and Miller, D. F.: Ohio J. Science **50**: 205, 1950.
37. Robbins, S. L., and Parker, F.: Endocrinology **42**: 237, 1948.
38. Robbins, S. L., and Parker, F.: New England J. Med. **241**: 12, 1949.
39. Robbins, S. L.: J. Clin. Endocrinol. **11**: 213, 1951.
40. Casas, F. F., Belizán, L., and Staffieri, J. J.: Bol. soc. obst. y. ginec. de Buenos Aires **26**: 229, 1947.
41. Sandoval, A. A. I.: Rev. cubana lab. clin. **2**: 191, 1948.
42. Haines, M.: Nature **162**: 416, 1948.
43. Haines, M.: Lancet **2**: 923, 1948.
44. Castillo, E. B.: Rev. méd. peruana **21**: 48, 1948.
45. Heredia, L. J.: Día méd. **20**: 2139, 1948.
46. Sandoval, A. I.: Rev. méd.-social san. benef. munic. **8**: 16, 1948.
47. Manstein, V. B., and Schmidt-Hoensdorf, F.: Deutsche. med. Wchnschr. **74**: 1258, 1949.
48. Herrera, J. M., Navarro, A. F. E., and de Herrera, C. L.: Arch. Hosp. Santo Tomás **4**: 120, 1949.
49. D'Arcy, E. N. S., and Grönwall, F. A.: New Zealand M. J. **48**: 572, 1949.
50. Vasconelos, F. C., and Leas, A. T.: Rev. brasil med. **6**: 236, 1949.
51. Sulman, F. G., and Sulman, E.: Harefuah **37**: 13, 1949.
52. Brody, H.: Am. J. Obst. & Gynec. **57**: 581, 1949.
53. Klopper, A., and Frank, H.: Lancet **2**: 9, 1949.
54. Mello, M. I.: J. Clin. Endocrinol. **9**: 1372, 1949.

55. de Aquino Salles, A., De Cenzo, M. A., and Baiocchi, O.: Med. cir. farm. **160**: 445, 1949.
56. Bhaduri, J. L., and Barahan, N. R.: Science **109**: 517, 1949.
57. McCallin, P. F., and Whitehead, R. W.: Science **109**: 518, 1949.
58. D'Arcy, E. N. S.: New Zealand M. J. **49**: 537, 1950.
59. Soucy, L. B.: Am. J. M. Technol. **16**: 6, 1950.
60. Gardner, H. L., and Harris, N. B.: AM. J. OBST. & GYNEC. **59**: 350, 1950.
61. Bell, D. M., Macgregor, J. W., and Vant, J. R.: Canad. M. A. J. **62**: 68, 1950.
62. Bieniarz, J.: Lancet **1**: 299, 1950.
63. Bettinger, H. F., and O'Loughlin, I.: M. J. Australia **2**: 40, 1950.
64. Bivens, M. D.: West. J. Surg. **58**: 238, 1950.
65. McCarthy, E. G., and Soucy, L. B.: Texas J. Med. **46**: 162, 1950.
66. Sulman, F. G., and Sulman, E.: J. Clin. Endocrinol. **10**: 932, 1950.
67. Sharnoff, J. G., and Zaino, E. C.: AM. J. OBST. & GYNEC. **59**: 653, 1950.
68. Jones, C. K., and Jones, H. W.: Am. J. Clin. Path. **20**: 289, 1950.
69. McCallin, P. F., and Whitehead, R. W.: AM. J. OBST. & GYNEC. **59**: 345, 1950.
70. Chu, W.: Am. J. Physiology **163**: 294, 1950.
71. Waldrop, E. G., and James, M. F.: South. M. J. **43**: 886, 1950.
72. Frazer, J. F. D., and Wohlzogen, F. X.: Brit. M. J. **2**: 330, 1950.
73. Greenblatt, R. B., Clark, S. L., and West, R. M.: Fertil. & Steril. **1**: 533, 1950.
74. Johnson, D. A.: California Med. **72**: 422, 1950.
75. Brede, H. D.: Klin. Wchnschr. **28**: 709, 1950.
76. Earle, K. V.: M. Press **223**: 602, 1950.
77. Felding, C. F.: Nord. med. **44**: 1745, 1950.
78. Szejnberg, L., and Rabau, E.: Gynaecologia **130**: 221, 1950.
79. de Moraes, P. A.: An. paulist. med. e. cir. **60**: 95, 1950.
80. Brazel, E.: Zentralbl. Gynäk. **72**: 527, 1950.
81. Parmentier, H.: Progr. méd. Paris **78**: 384, 1950.
82. Beckenback, W., and Paul, H.: Klin. Wchnschr. **28**: 79, 1950.
83. Pigeaud, H., Vincent, M., and Edelstein, L.: J. méd. Lyons **31**: 843, 1950.
84. Bedoya, J. M., and Puros, A.: Geburtsh. u. Frauenh. **10**: 492, 1950.
85. Wagner, J. W., and Shanahan, M. B.: J. M. A. Eire **26**: 60, 1950.
86. Goldzieher, J. W., Jordan, M. J., and Epstein, P. R.: Quart. Rev. Obst. & Gynec. **9**: 161, 1951.
87. Haskins, A. L., and Sherman, A. I.: AM. J. OBST. & GYNEC. **6**: 1150, 1951.
88. Reinhart, H. L., Caplan, I. J., and Shenowaros, G. Y.: Am. J. Clin. Path. **21**: 624, 1951.
89. Holyoke, J. B., and Hoag, E. F.: Am. J. Clin. Path. **27**: 12, 1951.
90. Lambeth, S. S.: J. Tennessee M. A.: **45**: 428, 1952.
91. Laubmann, M.: Zentralbl. Gynäk. **73**: 1818, 1951.
92. Thorborg, J. V.: Acta. endocrinol. **6**: 373, 1951.
93. Klahn, J.: Geburtsh. u. Frauenh. **11**: 753, 1951.
94. Dornes, W., and Saclisse, B.: Gerburtsh. u. Frauenh. **11**: 744, 1951.
95. Bromberg, Y. M., Brzezinski, A., Rozin, S., and Sulman, F. G.: Acta endocrinol. **7**: 31, 1951.
96. Forman, J. B., and Floyd, R. D.: AM. J. OBST. & GYNEC. **63**: 1352, 1952.
97. Hause, W. A.: AM. J. OBST. & GYNEC. **63**: 1356, 1952.
98. Mukherjee, C., and Saha, H.: J. Indian M. A. **21**: 335, 1952.
99. Frusch, W.: München. med. Wchnschr. **94**: 1620, 1952.
100. Farrant, P. C., and Buckland, F. E.: Lancet **2**: 990, 1952.
101. Schüller, E.: Wien. Med. Wchnschr. **102**: 922, 1952.
102. Lambeth, S. S.: J. Tennessee M. A. **45**: 428, 1952.
103. O'Hanrahan, I.: West. J. Surg. **60**: 589, 1952.
104. Hodgson, J. E.: J. A. M. A. **153**: 271, 1953.
105. Robbins, S. L., and Parker, F.: J. Clin. Endocrinol. **12**: 354, 1952.
106. Robbins, S. L., and Parker, F.: J. Clin. Endocrinol. **12**: 744, 1952.
107. Sobel, H., and Edelman, S.: Am. J. Clin. Path. **21**: 950, 1951.
108. Rugh, R.: Proc. Soc. Exper. Biol. & Med. **36**: 418, 1937.
109. Rugh, R.: J. Exper. Zool. **80**: 81, 1939.
110. Rugh, R.: Proc. Amer. Phil. Soc. **84**: 617, 1941.
111. Rugh, R.: The Frog, Philadelphia, 1951, The Blakiston Company.
112. Pinto, R. M., and Suer Boero, H. J.: Prensa méd. argent. **35**: 165, 1948.
113. Biesinger, D. I., and Miller, D. F.: Ohio J. Sc. **52**: 169, 1952.
114. Rugh, R.: Personal communication.
115. Frank, R. T., and Berman, R. L.: AM. J. OBST. & GYNEC. **42**: 492, 1941.
116. Berman, R. L.: AM. J. OBST. & GYNEC. **64**: 440, 1952.
117. Frank, R. T.: AM. J. OBST. & GYNEC. **43**: 729, 1942. (Correspondence.)

118. Ramsey, T. L., Falkenstein, A. P., and Siykowski, E. J.: J. Lab. & Clin. Med. **29**: 419, 1944.
119. Soman, D. W.: Indian M. Gaz. **79**: 68, 1944.
120. Zondek, B., Sulman, F., and Black, R.: J. A. M. A. **128**: 939, 1945.
121. Fried, P. H.: AM. J. OBST. & GYNEC. **54**: 689, 1947.
122. Behnken, E. W., Lloyd, C. W., and Hughes, E. C.: AM. J. OBST. & GYNEC. **56**: 930, 1948.
123. Riddell, R. J.: M. J. Australia **2**: 382, 1949.
124. von Massenbach, W.: Zentralbl. Gynäk. **7**: 849, 1949.
125. Farris, E.: Fertil. & Steril. **1**: 76, 1950.
126. de Aquino Salles, A.: An. brasil. ginec. **15**: 467, 1943.
127. Amoral, C. D.: An. brasil. ginec. **20**: 108, 1945.
128. Salmon, U. J., Geist, S. H., Salmon, A. A., and Frank, I. L.: J. Clin. Endocrinol. **2**: 167, 1942.
129. Kupperman, H. S., Greenblatt, R. B., and Noback, C. S.: J. Clin. Endocrinol. **3**: 548, 1943.
130. Kaminester, S.: AM. J. OBST. & GYNEC. **47**: 265, 1944.
131. Kline, B. S.: Am. J. Clin. Path. **14**: 265, 1944.
132. Kupperman, H. S., and Greenblatt, R. B.: South. M. J. **39**: 158, 1946.
133. Soman, D. W.: Indian M. Gaz. **81**: 134, 1946.
134. Bunde, C. A.: AM. J. OBST. & GYNEC. **55**: 317, 1947.
135. Riley, G. M., Smith, M. H., and Brown, P.: J. Clin. Endocrinol. **8**: 233, 1948.
136. Kelsey, J. F., Salmon, A. A., Davis, C. D., and Hamblen, E. C.: AM. J. OBST. & GYNEC. **60**: 904, 1950.
137. Hoffman, R. V., and Giordano, A. S.: Am. J. Clin. Path. **21**: 33, 1951.
138. Albert, A.: Proc. Staff Meet., Mayo Clin. **24**: 259, 1949.
139. Fried, P. H.: AM. J. OBST. & GYNEC. **57**: 868, 1949.
140. Fried, P. H., and Rakoff, A. E.: J. Clin. Endocrinol. **10**: 423, 1950.
141. Farris, E. J.: AM. J. OBST. & GYNEC. **48**: 200, 1944.
142. Kupperman, H. S., and Greenblatt, R. B.: J. M. A. Georgia **36**: 58, 1947.
143. Fried, P. H.: West. J. Surg. **56**: 552, 1948.
144. Fried, P. H.: AM. J. OBST. & GYNEC. **57**: 868, 1949.
145. Hofman, C.: Rev. franç. de gynéc. et d'obst. **47**: 212, 1952.
146. Fried, P. H., and Rakoff, A. E.: J. A. M. A. **141**: 25, 1949.
147. Sturgis, S. H., and Haour, P.: Fertil. & Steril. **2**: 347, 1951.

1078 MADISON AVENUE
NEW YORK 28, N. Y.

THE INCIDENCE OF YEASTLIKE ORGANISMS IN THE LOWER GENITAL TRACT OF PREGNANT FILIPINO WOMEN*

CARLYN HALDE, PH.D.,** SAN FRANCISCO, CALIF., AND
GLORIA T. ARAGON, M.D., MANILA, P. I.

(From the Department of Medicine, Stanford University School of Medicine, and the Department of Obstetrics, University of the Philippines College of Medicine)

THE predisposition of pregnant women to lower genital tract infection by *Candida albicans* has been a frequent observation by obstetricians. It is the purpose of this paper to study the incidence of yeastlike organisms in the lower genital tract of pregnant Filipino women, and to correlate such findings with complaints of pruritus vulvae and vulvovaginitis. While gynecological literature contains many reports on the causal relationship between mycotic infections and vulvovaginitis in pregnancy, this is the first study of this nature on Filipinas.

For many years, the study of yeastlike fungi was difficult because the differences in opinion concerning criteria to be used in classification seemed hopelessly confusing. Methods have been developed, however, which greatly facilitate classification, and the vast number of yeastlike, mycelia-producing, non-ascospore-forming fungi have been reduced to synonymy with comparatively few valid species in the genus Candida. The clinical name moniliasis for Candida infections was derived from the generic name Monilia, which was formerly used to describe these fungi.

Since species of Candida can be isolated from skin, the vagina, throats, and stools of apparently healthy people and from the sputum of patients with tuberculosis or other pulmonary diseases, the diagnosis of moniliasis is difficult. The appearance of lesions, the numbers in which the organisms are isolated, repeated examinations in which other etiological agents are excluded are necessary, at times, to warrant a diagnosis of moniliasis.

Candida may be seen in material taken directly from a lesion, as small (2 to 4 μ), oval, budding, thin-walled cells. Occasionally, threadlike filaments of mycelium are seen ramifying through the debris of epithelial cells. Clusters of budding cells may be found on some filaments.

Materials and Procedures Used

Mycological cultures were made on a series of 171 pregnant and 16 nonpregnant Filipino women. The majority of these women were seen at the Prenatal Clinic at the Philippine General Hospital. Only those women who

*Aided in part by a research grant E 786 from the National Microbiological Institute of the National Institutes of Health, Public Health Service.

**Fulbright student in the Philippines, 1950-1951.
Present address, University of California Medical Center, Los Angeles, Calif.

did not show any endocrinological or metabolic disorders or who did not have any gross pelvic pathology were chosen for this study. Thirty-three of the pregnant women and two of the nonpregnant women complained of pruritus vulvae.

The external genitals were cleansed with cotton swabs saturated with an antiseptic solution, with care that no solution entered the vagina. A sterile, nonlubricated speculum was carefully introduced halfway into the vagina, exposing the cervix and fornices. Sterile cotton swabs were then rubbed lightly on the surfaces of the posterior vagina and the cervix. The swabs were immediately placed in test tubes containing 5.0 c.c. of sterile water for subsequent transfer to culture media.

After the specimen had been taken, the hydrogen ion concentration at the surface of the posterior vagina was determined by the use of Alkacid pH paper. Any history of pruritus vulvae or clinical evidence of infection in each patient was noted.

Cultures were made by streaking the swabs across the surface of two Sabouraud's dextrose agar slants. These were incubated at room temperature for two weeks. As soon as growth of yeastlike colonies was noted, however, transfers were made to another tube of Sabouraud's dextrose agar for further identification. The method of Martin and associates[3] was used to classify the organisms which were isolated. Bacteriological cultures were not made. Ninety-seven of the specimens were examined as wet mount preparations under the microscope. The presence of yeastlike budding cells and *Trichomonas vaginalis* was recorded

Results

Yeastlike fungi belonging to the genera Candida, Saccharomyces, and Cryptococcus were isolated from 44 (25.7 per cent) of the 171 pregnant women. The results of this study may be seen in Table I. No mycotic organisms were isolated from the nonpregnant women.

TABLE I. THE PRESENCE OF MYCOTIC ORGANISMS IN THE VAGINAS OF PREGNANT FILIPINO WOMEN

ORGANISM ISOLATED	WITH PRURITIS		WITHOUT PRURITIS	
	NUMBER OF CASES	PER CENT	NUMBER OF CASES	PER CENT
C. albicans	10	30.3	2	1.45
C. tropicalis	3	9.0		
C. krusei			2	1.45
C. guilliermondi			2	1.45
C. stellatoidea			4	2.9
Cryptococcus sp.			7	5.0
Saccharomyces sp.			14	10.1
No organisms	20	60.6	107	77.5
Total	33		138	

Ten cases of vulvovaginitis caused by *C. albicans* were found among the 187 women studied. In addition, 2 women were found to harbor abundant *C. albicans* in the vagina but there was no complaint of pruritus nor did they show clinical evidence of infection. Three women who complained of pruritus vulvae were found to have infections caused by *C. tropicalis.* No mycotic organisms were isolated from the remaining women who complained of pruritus vulvae.

Among the 35 women who complained of pruritus vulvae, all 10 cases of *C. albicans* infections were observed during the third trimester of pregnancy. The 3 cases of *C. tropicalis* infection were observed during the third, fifth, and

ninth months of pregnancy, respectively. The pH of the vaginas of the women with proved mycotic vulvovaginitis was 5.0 to 6.0 with the exception of one woman in whom the pH was 4.5. In the remaining symptomatic women, the pH of the vagina in 3 women was 4.5, in 8 women, 5.0, and in 11 women, 6.0.

Numerous budding cells and usually some fragments of mycelium were seen in direct microscopic mounts of material taken from the vaginal swabs in all but 3 unexamined cases in which *C. albicans* and *C. tropicalis* were isolated. In 72.4 per cent of those cases in which some species of fungus grew, a direct microscopic examination of a smear from the vagina showed abundant yeastlike, budding cells. Fifteen per cent of the women from whom no yeasts were isolated showed the presence of a few yeasts in the microscopic mount.

Three species of Candida other than *C. albicans* and *C. tropicalis* were isolated. None of the women from whom these were recovered complained of pruritus vulvae or showed evidence of vaginal infection. These organisms were *C. krusei, C. guilliermondi,* and *C. stellatoidea.* These fungi have been considered as nonpathogenic saprophytes by Jones and Martin[2] and Conant and associates.[1]

Seven isolations of Cryptococcus species and 14 isolations of Saccharomyces species were obtained.

Trichomonas vaginalis, the protozoan parasitic to the vagina, was observed in 3 vaginal specimens among the 97 specimens which were examined microscopically. Two of the specimens in which Trichomonas were seen were from pregnant women who did not complain of pruritus vulvae nor show an abnormal vaginal wall. One of these cases was associated with the presence of *C. stellatoidea.* This parasite was recovered from the vagina of only one woman who complained of pruritus. Since many of the specimens were not examined immediately after they had been taken, the incidence of Trichomonas infestation may have been much greater.

Comment

The importance of mycotic infection as the cause of vulvovaginitis and pruritus vulvae in pregnant women is emphasized in this study, since 39.3 per cent of the cases observed showed abundant growth of *C. albicans* or *C. tropicalis* on culture.

It is also shown that the presence of yeasts within the vagina of pregnant women does not necessarily mean that they will develop vulvovaginitis. It has long been thought that the abundance of glycogen-like material in the vaginal epithelium of pregnant women is a predisposing factor for moniliasis. Apparently this material also serves as a desirable substrate for the growth of other species of yeasts which do not produce disease. Even *C. albicans* may be present without producing symptoms. Nearly one fourth (22.5 per cent) of the asymptomatic women studied had various species of yeasts present in the vagina. In those who complained of pruritus vulvae, however, only *C. albicans* and *C. tropicalis* were present. Most cases of vaginal moniliasis reported in medical literature were associated with *C. albicans.*

Candida tropicalis was found in 3 cases of pruritus vulvae. This fungus, ordinarily a saprophyte, may be pathogenic, although cases of infection due to it are extremely uncommon. This organism and the other yeasts reported in this study are often found as saprophytes on the mucous membranes and in

feces and sputum. The incidence of *C. tropicalis* causing pruritus vulvae in Filipino women is somewhat greater than that encountered in similar studies carried out in the United States.

Summary

Yeasts were isolated from the vaginas of 25.7 per cent of 171 pregnant Filipino women. Of 33 women complaining of pruritus vulvae during pregnancy, 39.3 per cent were found to have infections due to *Candida albicans* and *Candida tropicalis*.

References

1. Conant, N. F., Smith, D. T., Baker, R. D., Callaway, J. L., and Martin, D. S.: Manual of Clinical Mycology, Philadelphia, 1954, W. B. Saunders Company.
2. Jones, C. P., and Martin, D. S.: Am. J. Obst. & Gynec. **35**: 98, 1938.
3. Martin, D. S., Jones, C. P., Tao, K. F., and Lee, L. C.: J. Bact. **34**: 99, 1937.

MANAGEMENT OF URINARY-VAGINAL FISTULA IN 253 CASES*

VIRGIL S. COUNSELLER, M.D., AND FRANK H. HAIGLER, JR., M.D.,
ROCHESTER, MINN.

(From the Section of Surgery, Mayo Clinic and Mayo Foundation,† and the Section of Obstetrics and Gynecology, Mayo Foundation)

URINARY-VAGINAL fistulas seem to be increasing. Furthermore, there is a divergence of ideas regarding their surgical treatment. It seemed to us, therefore, that it would be of interest to record the types of fistulas and the methods of handling them on one surgical service. Our intention then is to report as accurately as possible on the management of 253 urinary-vaginal fistulas. The number of cases is sufficient, we believe, and the time interval (1933 through 1954) is great enough to permit us to arrive at some very definite conclusions about the results of treatment. It is hoped that this statement is not too dogmatic, but 21 years spent in one field of study of a particular entity is a reasonable period of experience and causes one to have some rather fixed ideas concerning management of that entity.

All during this period there were changing conditions to modify one's ideas: such conditions as acidification of urine to pH 4.5 or 5 by chemical means or by diet, the great advent of the control of infections, then the continued improvement of suture material and, finally, the methods of exposure of the fistula. All these contributed to better results and to better statistics.

The surgical technique of closing a fistula has been changed from time to time with improved results. Not so long ago it was felt that fistulas should be repaired longitudinally or perhaps with a purse-string suture. It is known now that it is faulty to use the purse-string method. Also, it is known now that fistulas should be repaired in many instances either transversely or in the direction in which the injury took place. It has been learned too that the method of approach to these fistulas must be selective, either vaginal or abdominal, depending entirely (1) on the location of the fistula, (2) on the number of previous attempts at repair, (3) on the amount of fixation of the vaginal wall, and (4) on whether or not the bowel has been involved also. These are the determining factors.

It seems to us extraordinarily significant that it has been just 103 years since 1852, when Sims[1] described his vaginal procedure and methods for cure of vesicovaginal fistula. In his day the fistulas were principally due to obstetric deliveries, but today that has changed. The cause of urinary fistulas now is surgical or traumatic rather than obstetric by a ratio of approximately 8 to 1.

---

*Presented at a meeting of the Miami Obstetrical and Gynecological Society, Miami, Fla., May 12, 1955.

†The Mayo Foundation, Rochester, Minn., is a part of the Graduate School of the University of Minnesota.

It would be well to repeat on this occasion the principles which Sims first advocated for cure of these fistulas. These are as follows: (1) The parts to be operated on must be brought into a clean or healthy condition by appropriate treatment. (2) Adequate exposure of the field of operation must be secured to enable employment of an accurate technique, this to be accomplished by means of the lateral prone position known by Sims' name. (3) No tension whatever must be placed on the edges of the wound when they are approximated, the surrounding tissues being loosened for that purpose. (4) Silver wire must be employed for the sutures. (5) The bladder must be kept continually free of urine by drainage through a self-retaining catheter. Sims determined that the bladder was not healed sufficiently until 15 days after operation, so that the catheter should remain in place that long. These statements were made and reported in the January, 1852, issue of the *American Journal of the Medical Sciences,* when Dr. Sims was living in Montgomery, Alabama. He later became the Chief Surgeon at the Woman's Hospital in New York City which was founded in 1855, a century ago. It is significant that our successes today in the management of these patients depend on our efforts to follow these basic principles in one way or another.

Sims did not claim priority for the first operation for vesicovaginal fistula, since this operation had been done by others some years before. He did, however, claim priority for three things with reference to the operation: (1) for the discovery of a method by which the vagina could be thoroughly explored and the operation easily performed; (2) for the introduction of a new suture apparatus, which lies embedded in the tissues for an indefinite period without danger of cutting its way out as did silk ligatures; and (3) for the invention of a self-retaining catheter which can be worn with the greatest of comfort by the patient during the whole process of treatment. It should be further emphasized that these facilities were directed toward a vaginal operation without anesthesia and without electric light. Sims' retractor was designed to expose the vagina, and the light rays of the sun were reflected into the vagina by a properly placed mirror.

We would now like to acquaint you with some of the characteristics of bladder tissue, the urethra, and ureter. The ureter is noted for its contractile ability, and by this one identifies it during difficult or radical abdominal hysterectomies. Also, in marked uterine prolapse which one usually cures by vaginal hysterectomy, the ureter makes its presence known by instant contraction when one irritates it. It is well known that the ureter tends to reconstruct itself when injured if it has adequate drainage and is splinted by a catheter or other means. Its blood supply is different from the blood supply of most structures and can be easily, and unnoticeably, disturbed or destroyed, which may result in sloughing of a portion of the wall of the ureter. The ureter may also become fixed by trauma or cellulitis, which will result in inadequate drainage and dilatation of the ureter and renal pelvis. When the contractile power of the ureter is gone so that it resembles a pipe or just a canal, its function is seriously interfered with and trouble can be expected in due time.

The urethra, on the other hand, has no such contractile power and no such regenerative power as the ureter or bladder, but it does withstand infections and trauma remarkably well, as we all know. When it is surgically attacked it heals quickly. Incontinence is produced if the urethra becomes rigid or distorted and in particular if the normal urethrovesical angle is disturbed.

The bladder tissue is, as the senior author has often stated, very friendly to the surgeon in that it possesses great power of regeneration, or perhaps it is better to say power of restoration. It will withstand much more trauma than other tissues of the body. Portions of the bladder can be excised and it will regain its former capacity in a few months; however, for it to function normally it must have freedom of contraction and expansion. At times, following repeated operations for closure of vesicovaginal fistulas, the base of the bladder becomes so rigid that although the fistula may be cured the patient remains completely incontinent.

The term "urinary-vaginal fistula" seems to me to be more appropriate than "vesicovaginal fistula," since the former term includes all of the types encountered. In Table I it is apparent that the most frequent type of fistula in this series is vesicovaginal. The second in frequency is urethrovaginal and next is ureterovaginal. That is about what one would expect.

TABLE I. TYPE OF FISTULA

TYPE OF FISTULA	NO. OF CASES
Vesicovaginal	184
Urethrovaginal	41
Ureterovaginal	14
Vesicourethrovaginal	8
Vesicocervicovaginal	3
Ureterovaginal and vesicovaginal	1
Vesicoureterocervicovaginal	1
Rectovesicovaginal	1
Total	253

These fistulas appear at all ages, with the largest number between the ages of 30 and 59 years. This corresponds to the greater frequency of surgical procedures on the reproductive organs in that age period. The traumatic injuries by automobile accidents cause these fistulas to appear at all ages, which in this series accounts for those patients in their teens, as shown in Table II.

TABLE II. AGE DISTRIBUTION

AGE (YEARS)	NO. OF CASES
0-9	1
10-19	2
20-29	21
30-39	56
40-49	108
50-59	51
60-69	13
70-79	1
Total	253

The kinds of surgical procedures which are complicated by the occurrence of urinary fistulas are quite numerous, as can be seen in Table III. The

decrease of obstetric fistulas is significant, and we are certain that today on large obstetric services it is most rare to have a urinary fistula. Those which are recorded here are referred from rural communities where adequate facilities are not always readily available for managing difficult obstetric problems.

TABLE III. CAUSES OF FISTULA

CAUSATIVE PROCEDURE	NO. OF CASES
Total abdominal hysterectomy	120
Obstetric	29
Vaginal repairs	27
Vaginal hysterectomy	18
Radiation treatment alone	9
Excision of bladder or urethral diverticulum	8
Abdominal removal of cervical stump	7
Transurethral resection	7
Abdominal hysterectomy with previous radiation	5
Trauma	4
Wertheim hysterectomy	3
Cauterization	3
Porro cesarean section	2
Amputation of cervix	2
Myomectomy	1
Wertheim hysterectomy with previous radiation	1
McIndoe operation for congenital absence of vagina	1
Miscellaneous surgical procedures	6
Total	253

Throughout the past 21 years there has been a decided increase in the proportion of surgical urinary fistulas. In the earliest report by the senior author[2] on these cases appearing at the Mayo Clinic, such fistulas constituted 66 per cent of all urinary fistulas, and in the most recent report in 1954 at the Mexican Urological Association,[3] the proportion was 92.3 per cent. That was the over-all picture of 567 vesical fistulas treated on all surgical services.

We believe it is the duty of surgeons to study the reasons why these surgical accidents occur during pelvic operation and to disseminate this information among our profession in order to try to prevent these complications.

Total abdominal hysterectomy is a much more common operation today than formerly. It heads the list in the production of fistulas. We believe that this complication is the result of three conditions: (1) the lack of adequate exposure, (2) bleeding and using many hemostats, and (3) an attempt to keep the vagina partially or completely closed with special forceps. In our opinion, the vagina should in nearly all instances be opened from behind and the cervix circumcised with moderately curved long-handled scissors. Then the vagina should be grasped by tenacula in four quadrants. By this method one does not sacrifice any of the vagina and the bladder and ureters are easily demonstrated.

We were surprised to find that the number of fistulas following repair of cystocele was about equal to the number of those occurring with vaginal hysterectomy. The reasons for these fistulas, we are convinced, are bleeding, the failure to ensure clean dissection of the bladder, and—the one major cause—the placing of a suture that penetrates the bladder mucosa. This will always produce a fistula in 8 to 10 days.

The very nature of a Wertheim hysterectomy predisposes both the bladder and the ureters to considerable trauma and destruction of the blood supply of the lower part of the ureters and the base of the bladder. Therefore, the incidence of fistulas in these cases is going to be proportionately higher. This is especially true if the patient has undergone a complete course of radium therapy to the cervix and a complete course of roentgen therapy.

Occasionally it becomes advisable to remove a cervical stump which has become diseased or prolapsed subsequent to supracervical hysterectomy. It has been our observation that the safest way to accomplish this is to remove the stump vaginally by the same method by which one would accomplish a vaginal hysterectomy. The abdominal removal is always more difficult than vaginal removal, and the possibility of trauma to the bladder or ureters is much greater. Seven fistulas, as can be seen in Table III, were produced by abdominal removal of a cervical stump.

A rather new type of vesicovaginal fistula has been appearing in recent years. That is one which occurs following transurethral resection of the neck of the bladder for urinary retention or obstruction. The difficulty arises from two sources as we see it. One is that it is difficult to estimate how much of the vesical neck should be resected, and the other is the control of bleeding, which is done by fulguration. This can easily destroy the thin layers of tissue remaining between vagina and bladder neck, resulting in a vesicovaginal fistula. Such a fistula is extremely difficult to repair owing to the damage of the tissues. Since there were seven cases in this series, we think this type of fistula should be emphasized.

Fistulas resulting from radiation therapy for carcinoma of the cervix are always serious problems. Attempts at repair should not be undertaken until sufficient time has elapsed to make sure that the cancer will not recur. This time interval is usually a minimum of 3 years. We continue to see a few of such patients, but the number seems to be decreasing. The problem becomes so much the more serious if the patient also has a rectovaginal fistula also caused by excessive radiation. Such a condition may be classified as inoperable if the patient is elderly. We are sure surgical treatment should not be advised unless one is certain the situation will be definitely improved, if not cured.

TABLE IV. ASSOCIATED UROLOGIC DISEASE*

CONDITION	NO. OF CASES
Nonfunctioning kidney	4
Vesical calculus or incrustations or both	9
Detached urethra	1
Pyelonephritis	8
Hydronephrosis	7
Perinephritis	1
Complete urethral stenosis	1
Carcinoma of bladder	1
Carcinoma of ureter	1
Acute cystitis	1
Reduplication of ureter and renal pelvis	1
Ureterectasis	1
Ureterocele	1

*Urologic diseases or complications arising secondary to the initial procedure here are not included but are listed elsewhere as "complications."

One should always be alert to any associated urologic conditions before proceeding with closure of the fistula. These, which usually are noted in a careful clinical examination, include inflammation, lack of function of one kidney, urethral obstruction or stenosis, vesical calculi and incrustations (Table IV). Various degrees of hydronephrosis on one or both sides often indicate a compromised ureter. A patient who has a cord bladder or a rigid vesical neck from trauma will be incontinent although the fistula is closed. The possibility of two openings to one fistula or two separate fistulas in the case is sometimes not considered. It can be a very likely possibility.

Operations which may be done in addition to closure of the fistula mostly concern the management of associated complications. Such operations were necessary in 67 patients of the 253 (Table V). If no complications exist it is best in general not to submit the patient to any elective operations. Her greatest desire is to be cured of the fistula. There are some instances, however, in which elective operations are indicated and should be performed.

TABLE V. ADDITIONAL SURGICAL PROCEDURES AT TIME OF REPAIR

PROCEDURE	NO. OF CASES
Reimplantation of ureter into bladder	9
Nephrectomy	6
Perineorrhaphy	6
Repair of cystocele	5
Repair of urethrocele	4
Removal of cervical stump	4
Trachelorrhaphy	4
Plastic operation on vagina	4
Colpoperineorrhaphy	3
Episiotomy	3
Vaginal hysterectomy	2
Puncture of ovarian cysts	2
Freeing and repairing of adherent loops of intestine	2
Salpingectomy	1
Total abdominal hysterectomy	1
Closure of vagina for colpocele	1
Uterine myomectomy	1
Fothergill operation	1
Miscellaneous minor procedures	8
Total	67

The most frequent additional surgical procedure in this series was the reimplantation of a ureter into the bladder, and the next was nephrectomy. When the ureter has been involved, the kidney may be normal, although the patient may have had some evidence of renal infection. If the kidney and ureter are normal the patient is entitled to reimplantation of the ureter. When the kidney of an obviously sick patient contains cortical abscesses nephrectomy should be performed provided the other kidney is normal.

Another maneuver which we feel is a great asset when the fistula is located high in the vagina is to open the cul-de-sac and search for any loops of bowel attached to the vault. These usually can be easily separated. A good view of the retained adnexa can also be had at this time. The senior author tries to do this routinely if he can, since it is valuable in mobilizing the bladder. Furthermore, a leaf of peritoneum is often available to place over the suture line of the bladder for added protection and healing.

When these patients with urinary fistulas present themselves for examination, we inquire first as to when the fistula occurred, what kind of operation has been done, and whether an attempt at repair of the fistula has been made. A little less than one-half of the patients in this series had no previous attempts at repair, but 138 had experienced from one to five or more repairs (Table VI). The influence of previous surgical closure of the fistula can hardly be overemphasized. Each operation produces more scar tissue and less blood supply, so that the incidence of failure to close the fistula becomes progressively greater with each attempt. Some patients have undergone vaginal operations with recurrence and then subsequently an abdominal operation with recurrence. We have observed over the years that adequate blood supply is most important for primary healing. Scar tissue in the bladder and vaginal wall does not heal any better than scar tissue elsewhere in the body. Therefore, complete excision of all scar tissue is a real necessity. When this is done, the opening in the bladder is considerably larger than before, but the interior of the bladder can be inspected and the ureters catheterized at this time if necessary. Moreover, with excision of the scar the bladder becomes more mobile and can be drawn out into the vagina for accurate repair. The time interval since the last attempted repair or since the primary operation that caused the fistula is, we feel, most important. We almost always insist that 3 to 4 months elapse between operations. (Under some conditions this can be modified.) This will permit all edema and inflammation to subside and will allow the greatest restoration of blood supply to the parts.

TABLE VI. PREVIOUS OPERATIONS ELSEWHERE FOR REPAIR OF FISTULA

HISTORY	NO. OF CASES	
No previous repairs		115
Previous repairs		138
One repair	54	
Two repairs	47	
Three repairs	17	
Four repairs	5	
Five or more repairs	15	
Total		253

TABLE VII. TYPE OF INITIAL REPAIR AND RESULT

	NO.	CURE	RECURRENCE
Direct Repair.—			
Vaginal	218	191 (88%)	27
Abdominal	5	5	0
Transvesical	1	1	0
Indirect Repair.—			
Ureterosigmoidostomy	7	7	0
Nephrectomy	9	9	0
Nephrostomy	4	4	0
Ureteral reimplantation	8	8	0
Closure of vagina	1	1	0
Total	253	226 (89%)	27

The type of surgical treatment depends entirely on the character of the urinary fistula, on its location, and on whether it is complicated or uncom-

plicated. Different types of repair are advised. In this series we designate them as "direct" or "indirect" repair. By direct repair we mean either vaginal, abdominal, or transvesical repair. By indirect repair we mean ureterosigmoidostomy, nephrectomy, nephrostomy, ureteral reimplantation, or closure of the vagina. We use all methods, as can be seen in Table VII.

We have for several years now advised the vaginal approach in the direct repair. We think we have good reasons for this. The majority of the fistulas are vesicovaginal, and when the fistula can be mobilized by the vaginal approach one can work with the injured tissues in plain view. Then, too, one should always remember that any convalescence from vaginal operations is much shorter and certainly less disabling than convalescence from abdominal operations. If there is a failure we are right back where we started from and the patient is no worse off except for time and expense. This is not quite the same after the abdominal or transvesical approach. If the fistula is high and cannot be exposed or if it is complicated by a rectovaginal fistula, the abdominal approach is the best. I am aware that many urologists advocate the transvesical approach routinely but it is hard for us to rationalize going through the top of an organ to repair a hole located in the bottom of it, especially if it can be reached from the underside vaginally. We are inclined to believe also that the female bladder which supports a suprapubic tube for a while is never completely comfortable later.

These methods of approach must be decided by the individual surgeon, and the method should be chosen which gives to his service the greatest success. In this connection we are sure that it is incorrect to advocate a routine operation. The indications should fit the particular situation. In Table VII we show how the patients in this series have been treated, the greatest number undergoing vaginal repair with a primary-cure rate of 88 per cent, a rate which is especially noteworthy when one considers that more than half of these patients had undergone repair previously from one to five or more times.

Some of the cases are not suitable for direct operations, such as large vesicovaginal fistulas resulting from radiation; also, cases where there is a badly damaged kidney with infection and those in which a ureterovaginal fistula is situated near the ureterovesical orifice. When the bladder is so damaged that it is incapable of holding urine, then a bilateral ureterosigmoidostomy or some other operation to produce urinary diversion is indicated. These operations we call "indirect operations." There were 29 of these patients on whom indirect operations were performed and all were cured, in the sense that they were not leaking urine. To be sure, it is not a perfect situation, but the patient is comfortable and is restored to quite normal life. The best of these cases is the successfully reimplanted ureter.

Some of the technical problems and difficulties are a bit clearer if we study the patients who had recurrences and subsequent operations. This situation is illustrated in Table VIII. Four of the patients with recurrence after the initial repair did not return to us for subsequent treatment. Of the 22 patients operated on by the vaginal approach at the second operation, we cured 9 but failed to cure 13. One patient was cured by the indirect method. Then in 5

of these 13 patients we performed indirect operations, since it seemed impossible to accomplish relief in any other way. We attempted the vaginal approach a third time in 8 of the 13 cases and failed in all 8. One patient was cured by urinary diversion at the fourth attempt, and we tried the vaginal approach in 7 and cured only one. We tried the vaginal approach the fifth time in the other 6 patients and cured one. It did not seem advisable for the 5 remaining patients to undergo further surgical procedures.

TABLE VIII. SUBSEQUENT TREATMENT OF RECURRENCES IN 23* PATIENTS

PROCEDURE	NO. OF PATIENTS	CURE	RECURRENCE
Second Operation.—			
Vaginal	22	9	13
Indirect†	1	1	0
Third Operation.—			
Vaginal	8	0	8
Indirect†	5	5	0
Fourth Operation.—			
Vaginal	7	1	6
Indirect†	1	1	0
Fifth Operation.—			
Vaginal	6	1	5
Indirect†	0	0	0

*Four additional patients had recurrences but had no subsequent treatment here.
†Indirect = urinary diversion.

It is apparent that we use all methods of direct approach, but we try to be most careful in our selection and not to put the patients to any more inconvenience than we feel absolutely necessary for curing the fistula.

We feel that when the vaginal approach is used the scar tissue in the vaginal wall should be excised anteroposteriorly and the scar tissue of the bladder wall should be excised in the direction in which the defect has developed. Exposure of the fistulous area is best demonstrated by placing the patient on her abdomen and elevating the buttocks by any method one chooses. We place the patient on a Pender frame which is so constructed and padded that the patient is not traumatized. By placing a Sims speculum against the perineum an excellent view of the fistula can be obtained.

The closure should always follow the direction of the fistula, which may be anteroposterior, diagonal or transverse. In recent years we have found that more often it is far safer to repair the fistula transversely than in any other direction. The vaginal wall is then repaired anteroposteriorly.

The suture material is all absorbable catgut and of small caliber. The point of importance of this closure is that it resembles the type of suturing that is done in an enteroanastomosis to prevent leakage. The second row of sutures begins at least 1 cm. before the beginning of the first row of sutures and ends at least 1 cm. beyond the end of the first row. The third row begins and ends similarly in relation to the second row. The suturing is done in such a manner as to leave no dead space, to pick up adequate amounts of bladder wall, but not to shut off circulation.

There is no operation that is free from complications, but the mortality rate in the surgical treatment of fistulas is extremely small. When complica-

tions do occur in operations on urinary vaginal fistulas it is almost always in those difficult cases in which there are recurrences and a diseased urinary tract. These complications come regardless of the direct or indirect procedure. The percentage of complications is much greater in the direct abdominal approach than in the direct vaginal approach. It is approximately 6 to 1 (Table IX). The deaths of the 2 patients were not related to the surgical procedure per se. The number and character of the complications are noted in Table X.

TABLE IX. POSTOPERATIVE COMPLICATIONS

OPERATION	NO.	COMPLICATIONS	PER CENT
Direct Procedure.—			
Vaginal	250	14	5.6
Abdominal	13	4	30.8
Indirect Procedure.—			
Urinary diversion	29	3	10.3
Total	292	21	7.2
POSTOPERATIVE DEATHS			
Patients	253		
Procedures	292		
Deaths	2 (neither related to operation itself)		

TABLE X. POSTOPERATIVE COMPLICATIONS

COMPLICATION	NO. OF CASES
Thrombophlebitis (vaginal technique)	3
Thrombophlebitis (abdominal technique)	2
Pulmonary embolism (vaginal technique)	3
Pulmonary embolism (abdominal technique)	1
Ureteral obstruction requiring nephrostomy (vaginal technique)	2
Ureteral obstruction requiring ureterosigmoidostomy (vaginal technique)	1
Pyelonephritis and perinephritic abscess requiring nephrostomy (indirect procedure)	1
Infected wound (abdominal technique)	1
Dermatitis medicamentosa or allergy (?) or both (vaginal technique)	2
Brain abscess (indirect procedure)	1
Fecal fistula (indirect procedure)	1
Acute cerebral edema (?)—death 16 hours postoperatively (vaginal technique)	1
Ureterovaginal fistula (vaginal technique)	1
Urinary-tract infection* (vaginal technique)	1

*Considered only if temperature was above 100.4° F. for 3 or more consecutive days and other causes were ruled out.

In conclusion, we hope that we have given some information which will be useful in managing surgical problems of this nature, having given our methods and results in 253 cases as they occurred on one surgical service.

References

1. Sims, J. M.: Am. J. M. Sc. 23: 59, 1852.
2. Counseller, V. S.: Vesicovaginal Fistula. Read at the University of Texas, Medical Branch, Post Graduate Course in Obstetrics, Galveston, Texas, March 11 and 12, 1948.
3. Counseller, V. S., and Hunt, William: Surgical Management of Vesicovaginal Fistulas. Read at the meeting of the Mexican Urological Association, Mexico City, Mexico, May 2 to 10, 1954.

EXPERIMENTAL EVALUATION OF THREE TYPES OF END-TO-END URETEROURETERAL ANASTOMOSIS

N. S. R. MALUF, M.D., AND BÉLA HALPERT, M.D., HOUSTON, TEXAS

(From the Section of Urology, the Department of Surgery, and the Department of Pathology, Baylor University College of Medicine and Veterans Administration Hospital, Houston, Texas)

A KIDNEY is not infrequently deliberately sacrificed when the ureter has been inadvertently severed during a difficult procedure in the pelvis. This may be due to lack of confidence in ureteroureteral anastomosis. The experiments herein recorded with the canine ureter indicate that ureteroureterostomy, with modern suture material and with use of a narrow splint of pure polyethylene, should be viewed with more optimism as to outcome.

Methods

Mongrel dogs weighing 7.8 to 12.7 kilograms were quarantined for at least two weeks before use. Anesthesia was by pentobarbital sodium (about 30 mg. per kilogram, intravenously). Since the normal ureter of a medium-sized dog is too narrow to test the efficacy of multiple sutures for anastomosis, enlargement of the ureter was effected by distal obstruction. The peritoneum was entered through the caudal third of the linea alba. A flat strip of tantalum, 0.015 inches thick, about 0.75 cm. broad, and 2 cm. long, was clamped over the distal end of the right ureter about 2 cm. from the bladder with the aid of a needle-holder, so as partially to occlude the ureter. The strip was clamped just tightly enough to prevent its sliding along the ureter. Ten to fourteen days after application of this clamp, the peritoneal cavity was again entered through an identical incision. The tantalum strip was opened and removed and the now mildly to moderately enlarged ureter was completely divided transversely about 3 cm. proximal to the segment on which the clamp had been applied. Usually the ureter had enlarged to about the caliber of the normal ureter of a human adult. The tantalum strip, as such, does not produce grossly evident inflammatory reaction or fibrosis. This was demonstrated in control animals in which the tantalum was applied about the ureter but left fairly loose. Fibrous connective tissue proliferation and cellular infiltration, however, occurred about the tantalum when the latter was applied tightly, as in the definitive experiments. This reaction was thus probably a response to compression of the ureter. Sections taken through the region of the ureter which had been clamped in a group of animals (H series) which were sacrificed on the tenth to twelfth day after snug application of the clamp and examined microscopically, disclosed that the tunica muscularis was encased in a hemorrhagic zone covered by connective tissue and infiltrated by inflammatory cells. The tunica muscularis, the tunica propria, and the urothelium were intact. Several urothelial cells in a state of division were seen in an entire cross section; these were not seen in the normal, unenlarged ureter.

Only end-to-end anastomosis was considered for reunion of the divided ureter because this, if properly executed, would be least likely to block ureteral

peristalsis. No drains were used. Six dogs were used for each of the three types of anastomosis. All animals survived without morbidity and showed no leakage through the incision. In Type I (E series) the ureteral ends were apposed by sutures of No. 5-0 chromic catgut swaged to a round needle and applied about 1 mm. apart. Most of the sutures were extra urothelial. Three to four guy sutures were introduced through and through. A total of eight to twelve sutures were applied in each anastomosis. After the lapse of eight to twelve weeks, intravenous pyelograms were obtained and the animals were sacrificed.

In Type II (F series) the ureteral ends were apposed by two to four through-and-through sutures of No. 5-0 chromic catgut swaged to a round needle over a tube or "splint" of animal-tested, practically reaction-free polyethylene.* The splint was 1.0 to 1.2 mm. in outer diameter (or 3 to 4 F.); that is, wide enough to accommodate urinary flow but not so wide as to stretch the ureter. The splint extended cephalad almost to the kidney and caudad into the bladder. It was sutured to the wall of the urinary bladder by No. 5-0 chromic catgut. After the lapse of three to four weeks intravenous pyelograms were obtained and the splint removed through a small incision in the bladder. The bladder was then closed with inverting extraurothelial sutures of cotton. Four to six weeks later, intravenous pyelograms were again taken and the animals sacrificed.

In Type III (G series) the procedure was identical with Type II except that the ureteral ends were apposed over the splint by multiple closely set sutures, mostly extraurothelial. Eight to twelve sutures, about 1 mm. apart, were used. Intravenous pyelograms were taken after the lapse of three to four weeks when the splint was removed, and again four to six weeks later at which time the animals were sacrificed.

Paraffin sections, stained with hematoxylin and eosin, were obtained as follows: (a) transverse sections of the right ureter proximal and distal to the anastomosis; (b) longitudinal sections through the anastomosis; (c) transverse sections of the left ureter at a level corresponding to that of the right ureter proximal to the anastomosis. Duplicate sections were prepared with Masson's trichrome stain to differentiate clearly connective tissue (blue) from muscle (red). Photographic records were taken of the anastomosis immediately after the animal was sacrificed and usually after excised ureter was slit longitudinally at the anastomosis.

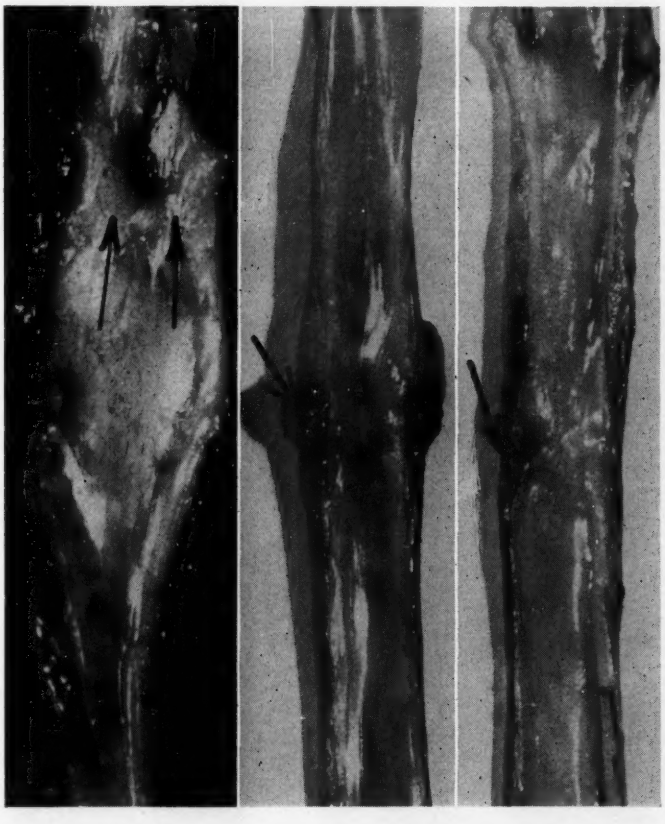
Results

The anastomosis was graded thus: (a) according to freedom from contracture or stenosis, from 1 to 4, the 4 implying absence of stenosis; and (b) according to freedom from muscular defect, from 1 to 4, the 4 implying complete broad union of the tunica muscularis without appreciable intervening connective tissue (Table I). Complete absence of stenosis was present in five ureters: two in Type I (E series), one in Type II (F series), and two in Type III (G series). The over-all results were fair to excellent. Type III (Figs. 3, 4, and 5, *B*) gave best results and Type II (Figs. 2 and 7, *A* and *B*) was least satisfactory from the standpoint of degree of stenosis (Table I and Figs. 1 to 5). The excellent apposition and the freedom from stenosis in those in which no splint was used, i.e., in Type I anastomosis, were remarkable (Fig. 1). This was true even in the unique subject in which the ureter had dilated massively prior to the anastomosis. The least satisfactory results with regard to extent of stenosis occurred in Type II (F series), in which union was probably partly by secondary intention owing to too few sutures, in spite of a splint (Figs. 2 and 5, *A* and *C*). In Type III (G series) apposition of the cut margins was precise,

*Product of Clay-Adams Co., 141 East 25th St., New York 10, N. Y.

with multiple closely set extraurothelial sutures and, in addition, use of a fine polyethylene splint (Figs. 3 and 4 and Fig. 5, *B*). In the Type III series, muscular apposition with minimal intervening connective tissue was superior (Table I and Fig. 5, *B*). Broad union of the muscularis at the anastomosis occurred in only one animal and this in the Type III series (Fig. 5, *B*).

In all instances the renal pelvis was dilated and some renal atrophy was present in accordance with the degree of dilatation and thickening of the ureter. This was the result of application of the tantalum clamp to the ureter during the initial ten to fourteen days. At the time the animals were sacrificed, dilatation and thickening of the ureter were quite as extensive distal to the anastomosis as proximally and thus were not due to obstruction at the anastomosis (Fig. 1). Obstruction of the ureter for ten to fourteen days was sufficient to produce incompletely reversible changes; in two animals these were extreme and resulted in rupture of the circular muscular coat of the ureter. In most instances, however, the extent of regression of the ureter toward normal was remarkable and indicated freedom from stenosis at the anastomosis.



A. *B.* *C.*

Fig. 1.—Type I anastomosis (arrows). Right ureter is slit longitudinally. *A*, dog E-1; *B*, dog E-5; *C*, dog E-6.

Intravenous pyeloureterograms taken under Nembutal anesthesia prior to sacrifice of the animals usually showed a break in the column of iodide at the site of anastomosis in all three types. In the absence of frank stricture this may be construed to be due to relative indistensibility of the ureter at the anastomosis.

Behavior of the ureter immediately after removal of the clamp was studied in another group of dogs (H series). In these, laparotomy was performed under

A. *B.* *C.* *D.*

Fig. 2.—Type II anastomosis (arrows). Right ureter is slit longitudinally. *A*, dog F-1; *B*, dog F-2; *C*, dog F-7; *D*, dog F-6. In panel *C* the polyethylene splint is shown. *sp*, and the left ureter, *lu*, for comparison with the right. In panel *D* the left ureter is sutured for comparison with the right.

TABLE I

DOG	FREEDOM FROM CONTRACTURE	FREEDOM FROM MUSCULAR DEFECT
E-1	3	-
E-2	4	-
E-3	4	2
E-4	3	1
E-5	3	3
E-6	3	2
Average	3.3	2.0
Mean deviation	0.43	0.5
F-1	3	3
F-2	2	2
F-3	2	2
F-5	2	3
F-6	2	3
F-7	4	3
Average	2.6	2.8
Mean deviation	0.7	0.4
G-1	3	4
G-2	3	3
G-3	4	3
G-4	3	3
G-5	4	3.5
G-6	3	3
Average	3.3	3.2
Mean deviation	0.4	0.3

A. *B.*

Fig. 3.—Type III anastomosis (arrows). Right ureter is slit longitudinally. *A*, dog G-3; *B*, dog G-4.

pentobarbital sodium anesthesia and diuresis forced by rapid intravenous drip of 10 per cent dextrose in water (1,000 c.c. in one-half hour). These dogs had intact ureters not operated upon except for the small segment of compression injury produced by the clamp. The ureteral peristaltic fluid wave passed readily across the site which had been clamped without accumulating in the region immediately proximal or distal to the site of clamping. The ureter dilated and

peristalsis progressed rapidly in a cephalocaudal direction uninterrupted. The small segment which had been clamped was quiescent but did not seem to interrupt the peristaltic wave. In no instance did the ureter remain permanently dilated during diuresis. The whole ureter dilated and then a peristaltic wave progressed rapidly down the ureter. There were up to seven such peristaltic waves a minute.

Fig. 4.—Type III anastomosis (arrows). Right ureter of dogs G-5 (left side of picture) and G-6 (right side of picture) is slit longitudinally. *sp*, splint.

It is noteworthy that removal of the splint three to four weeks after the anastomosis resulted in recession of hydronephrosis in the Type III (Fig. 6, dog G-2); whereas removal of the splint in the Type II series, after the same postoperative interval, resulted in augmentation of hydronephrosis (Fig. 7, dog F-1). This is correlated with the greater incidence of stenosis in the Type II

anastomosis, F series (Table I), and is probably the result of healing partly or largely by second intention in Type II compared with primary healing in Type III.

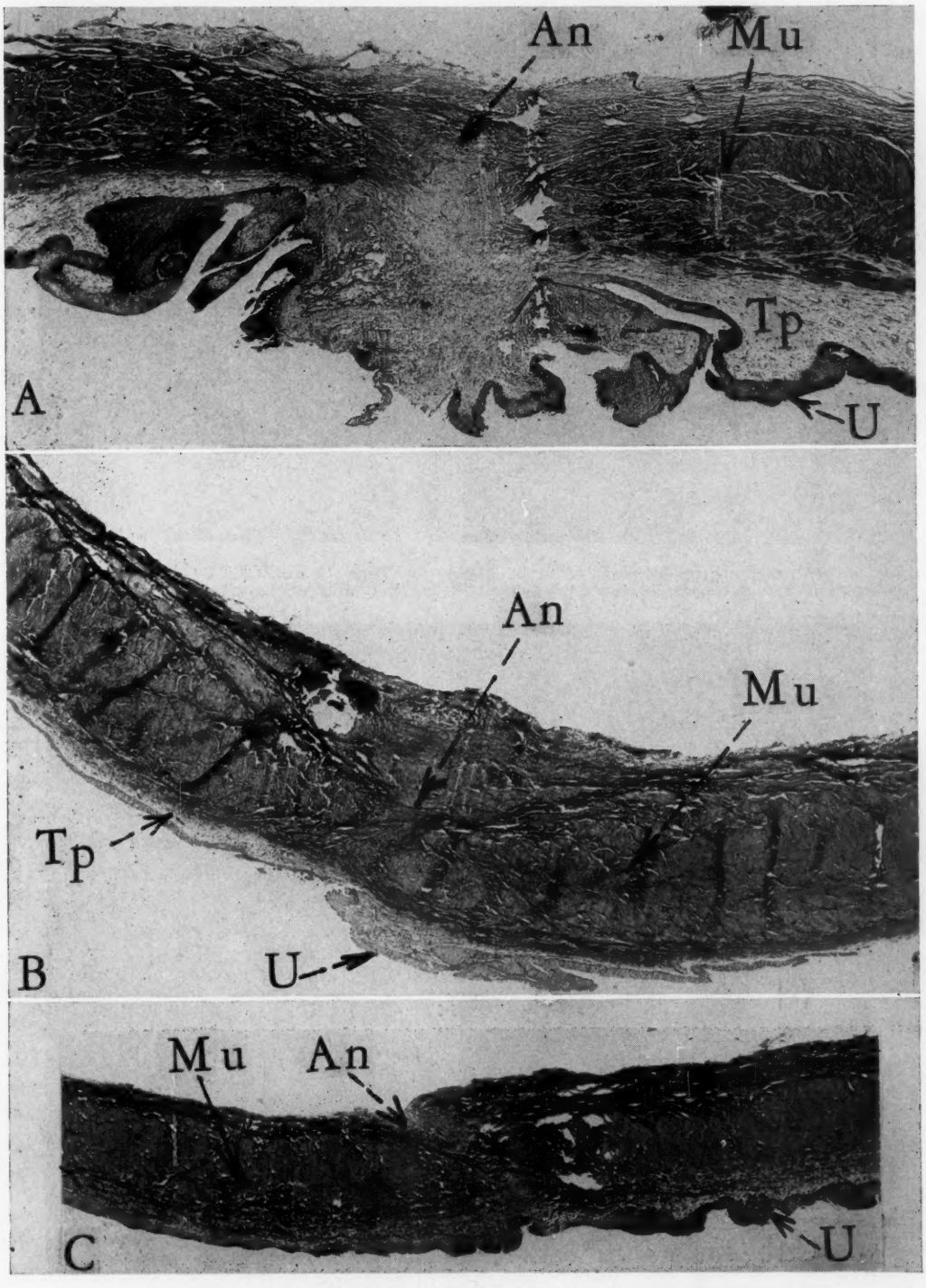


Fig. 5.—Photomicrographs of site of anastomosis, *An*, under low power. Only one wall of the ureter is shown. *Mu*, muscularsis; *Tp*, tunica propria; *U*, urothelium. *A*, dog F-2; *B*, dog G-1; *C*, dog F-7.

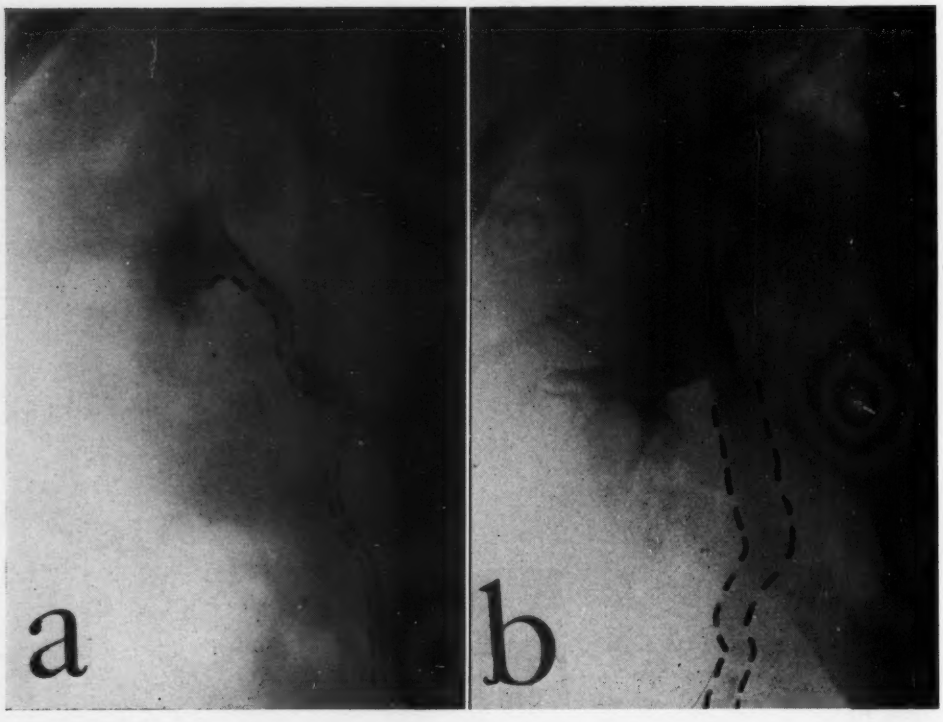


Fig. 6.—Intravenous pyelograms of right kidney in Type II anastomosis. *A*, dog F-1, immediately before removal of ureteral splint; *B*, dog F-1, four weeks after removal of splint.

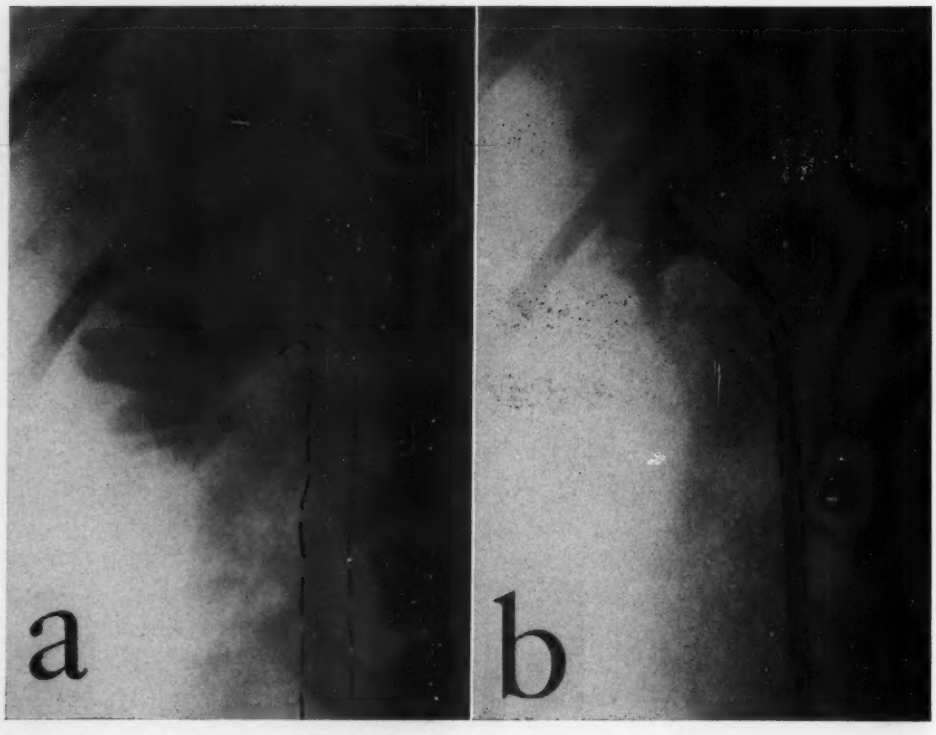


Fig. 7.—Intravenous pyelograms of right kidney in Type III anastomosis. *A*, dog G-2, immediately before removal of ureteral splint; *B*, dog G-2, four weeks after removal of splint.

No localized thickening of the ureteral lining and no intraluminal projection from the ureteral wall were present anywhere along the proximal portion of the ureter, where the tip of the polyethylene splint had been lying for four weeks. Lord and Eckel[19] reported an intraluminal projection from use of a Vitallium splint.

Commentary

1. Historical Background.—Inadvertent division or ligation of a ureter occurs most often during excision of diseased female reproductive organs. Hence, anastomosis of the severed ends of a ureter was first performed, in the late nineteenth century, by gynecological surgeons. There were then no pyelography, no chromicized catgut, and no minimal-trauma suture swaged to the needle. Unless there were a postmortem examination, a "good result" merely meant that the patient was asymptomatic and was not draining urine through the incision.

Parenthetically, absence of symptoms does not imply freedom from stricture at anastomosis. Thus, Douglas and Birnbaum,[8] of the New York Lying-In Hospital, noted that several of their cases with postoperative hydronephrosis, due to edema and other causes following radical hysterectomy, "were asymptomatic and the alterations in the urinary tract would never have been discovered without routine postoperative studies." Similarly, McKay, Baird, and Justis[21] remarked that if everybody doing pelvic surgery followed their cases closely "many kidneys would be saved."

Reviews on ureteroureterostomy have been compiled by Boari[3] and Alksne.[1] Schopf[26] appears to have been the first to reunite a severed ureter end to end. In the first case he used eight interrupted extraurothelial sutures of silk. He did not use a splint but advised one. The patient died several weeks later from pulmonary tuberculosis. Necropsy disclosed a stenosed anastomosis. In another case, he united the ureteral ends over a catheter which was passed into the bladder and out through the urethra. He believed that it was important to keep urine away from the healing anastomosis, a concept which our Type I series, without splint, refutes. Poggi[24] sutured the proximal segment of ureter to the distal after forming an intussusception of the former into the latter for a short distance. Cushing[6] wrote that "the ends of the severed ureter were found and united by two fine silk sutures and one of catgut. There was discharge of a little urine from the wound for some weeks, but the fistula promptly closed, forming a rare, if not unique, incident in the surgery of the ureter." Success was assumed. Tauffer[30] remarked that "it is striking to what slight extent specialists express themselves, in the literature, on the problem of ureteral injury; in the majority of cases severing the ureter is taken as established indication for extirpation of the kidney." Kelly[15, 16] reported an end-to-side pull-through ureteroureterostomy with use of silk sutures. This method of Van Hook[31] was then tried by Bloodgood[2] on dogs without resulting in hydroureter or stricture. Its disadvantage was the occurrence of an inevitable ureteral pocket above the anastomosis. Alksne[1] experimented on dogs and recommended the oblique end-to-end anastomosis of Bovée.[4] The end-to-end and end-to-side pull-through techniques gave good

results in dogs in spite of the smallness of the ureters and were thus considered better adapted to difficult conditions than the end-to-end apposition. Markoe and Wood[23] used Poggi's technique of drawing the proximal segment of ureter into the distal; the former, however, used a splint—a No. 9 catheter—which was passed through the urethra and removed after five days.

2. Use of a Splint.—Credit for anastomosing the severed ureteral ends over a splinting catheter goes to Schopf[26] who used a splint in his second case. Van Hook,[31] Kelly,[14] Bloodgood,[2] Poggi,[24] Bovée,[4] Boari,[3] and others reunited severed canine ureters without splinting and obtained good results. Cushing,[6] Kelly,[14-16] and Winslow[32] had satisfactory results symptomatically at least without splinting. Tauffer[30] and Markoe and Wood[23] splinted but Tauffer withdrew the splint immediately after completing the anastomosis. Alksne[1] stated that lack of the indwelling ureteral catheter was often due to its unavailability at the time of the accidental surgical injury or to fear of loss of the catheter in the bladder. Alksne theorized that a splint would be suitable because it would prevent damming of urine at the suture line, immobilize the ureter, and inhibit growth of granulation tissue into the lumen of the ureter. As to the first supposition, a plugged splint may be worse than no splint at all. The third supposition is negated by the present work in which growth of granulation tissue into the lumen of the ureter was most conspicuous in the Type II anastomosis (F series), in which a splint was used but in which only few apposing extraurothelial sutures were applied (Fig. 2 and Fig. 5, *A*).

A case which should be characteristic of the modern era was reported by Sisk.[28] He used fine chromic sutures swaged to a minimal-trauma needle, a pure polyethylene splint, and intravenous pyelography for control. The ends of the severed ureter were anastomosed end to end with fine chromic catgut extraurothelial sutures, with a 6 F. regular ureteral catheter used as a splint. There was no leakage at the drain. The catheter was removed on the tenth postoperative day. Intravenous pyelography showed an excellent result. McArthur[20] and Higgins[9] used a splint to advantage in remarkable ureteroureteral anastomoses. In his studies on ureterocolostomy, Hinman[11] found that splints wide enough to maintain the ureter under stretch produce necrosis of the ureter. Priestley[25] advised splinting with 10 to 14 F. (3.3 to 4.6 mm. outer diameter) soft rubber; polyethylene was not available then. He considered splinting valuable in maintaining an adequate lumen of the ureter at the site of anastomosis and in discouraging angulation of the ureter. He advised splinting for at least three weeks. Lord and Eckel[19] splinted the canine ureter with Vitallium tubing. Healing was primary without leakage of urine; stricture was minimal or absent. There was slight thickening of the lining of each ureter with a titlike projection where the lower end of the Vitallium tube contacted the urothelium. This may have been due to relatively wide tubing (3 mm. outer diameter). For the constricted ureter, Davis, Strong, and Drake,[7] who performed experiments on dogs, stated that the splint should be as large as possible because "experience shows that even if it fits the ureter fairly tightly, anemic necrosis does not occur." They used rubber tubing and did not mention the intraluminal projections noted

by Lord and Eckel. Ingraham and co-workers[12] have found that pure polyethylene, i.e., without plasticizer or antioxidant, elicits practically no inflammatory reaction.

Sutherland, Brown, Atkinson, and Birmingham[29] experimented with end-to-end apposition of the canine ureter over a polyethylene splint without sutures. Removal of the splint as early as the eleventh postoperative day resulted in complete stenosis; removal of the splint between the fourteenth and nineteenth postoperative days resulted in mild to moderate stenosis. This is corroborated by our work showing increase in hydronephrosis upon removal of the splint at three to four weeks in our Type II subjects but improvement in our Type III subjects. In the Type II anastomosis the ureteral ends presumably united to some extent by second intention whereas closely set extraurothelial suturing in the Type III anastomosis fostered early direct union.

3. The Modern Period.—In 1929 Iselin[13] of Paris pointed out that "it is almost an axiom, at least to French and German urologists, that once the ureter has been severed the kidney is for all practical purposes an irreparable loss. . . . Marion and Legueu even go so far as to state that suture of the ureter is not only useless but distinctly dangerous in view of the high percentage of infectious complications."

Advent of excretory pyelography in the 1930's necessitated a more critical appraisal of ureteroureteral anastomosis. Sisk[28] noted that "suddenly confronted with the problem of dealing with a severed ureter many surgeons adopt the procedure of ligation as the best way out of the dilemma. The ligation of a cut ureter under circumstances favorable to repair should receive our most severe condemnation." Old age, debility, and low financial station, as such, are no longer excuses for nephrectomy instead of anastomosis. Old persons, typically, have reduced differential renal function as shown by Lewis and Alving,[17] Lich,[18] and Shock,[27] among others. Conservation of the kidneys even in old age should thus be a urological tenet, provided upholding it does not endanger life.

4. Ureteroureterostomy for Congenital Defects.—Precision ureteroureterostomy will probably be important in the congenitally dilated, lengthened, corkscrew ureters, secondary to stenosis at the ureterovesical junction. Stenosis at this site is a common congenital defect according to Campbell[5] and others. Rather than mobilizing the redundant ureter, dividing it distally, and reimplanting it into the bladder, it may be preferable to incise the superior wall of the intramural ureter longitudinally transvesically, then unite the cut margin of the intramural ureteral lining to that of the bladder by fine sutures, and to excise an appropriate length of lumbopelvic ureter followed by ureteroureterostomy, according to the Type III anastomosis described in this paper. Hinman[10] has produced precedent in such cases for excision of redundant lumbopelvic ureter with reunion of the cut ends.

Summary

1. The distal end of the right canine ureter was partially obstructed by a tantalum clamp to increase its diameter to approximate that of the human ureter.

2. Ten to fourteen days later the clamp was removed and the now enlarged ureter was divided 2 to 3 cm. proximal to the site of clamping. The ends were reunited end to end by one of three ways.

3. In Type I, the ureteral ends were apposed by No. 5-0 chromic catgut sutures, mostly extraurothelial, 1 mm. apart.

4. In Type II, the ends were apposed on a fine polyethylene splint by two to four through-and-through No. 5-0 chromic sutures. The splint was removed after three to four weeks and the dogs sacrificed one to two months later.

5. In Type III, the ends were apposed over a fine polyethylene splint by No. 5-0 chromic sutures, mostly extraurothelial, 1 mm. apart. The splint was removed after three to four weeks and the dogs sacrificed four to six weeks later.

6. Using extent of muscular apposition and freedom from stenosis as criteria, Type III excelled. Results of Type I were very good and of Type II moderate. None of the animals died and none showed drainage through the incision. The ureters were equally dilated distal and proximal to the anastomosis.

7. The splint did not produce intraluminal growth or stricture where it formed contact with the ureter at its free proximal end.

References

1. Alksne, J.: Folia urologica **3**: 281, 340, 1908.
2. Bloodgood, J.: Remarks After Kelly's[14] paper.
3. Boari, A.: Chirurgia dell 'Uretere. Studio sperimentale e Clinico. Roma, 1900, Societa Editr. Dante Alighiere.
4. Bovée, J. W.: Ann. Surg. **25**: 51, 1897.
5. Campbell, E. W.: J. Urol. **60**: 31, 1948.
6. Cushing, E. W.: Ann. Gynaec. & Pediat. **7**: 277, 1893.
7. Davis, D. M., Strong, G. H., and Drake, W. M.: J. Urol. **59**: 851, 1948.
8. Douglas, R. G., and Birnbaum, S. J.: South. M. J. **47**: 559, 1954.
9. Higgins, C. C.: Trans. Am. A. Genito-Urin. Surgeons **27**: 279, 1934.
10. Hinman, F.: Arch. Surg. **18**: 21, 1929.
11. Hinman, F.: VII Congrés Internat. Soc. Urol., p. 464, 1939.
12. Ingraham, F. D., Alexander, E., and Matson, D. D.: J. A. M. A. **135**: 82, 1947.
13. Iselin, M.: Surg., Gynec. & Obst. **49**: 503, 1929.
14. Kelly, H. A.: Bull. Johns Hopkins Hosp. **4**: 89, 1893.
15. Kelly, H. A.: Ann. Surg. **19**: 70, 1894.
16. Kelly, H. A.: Operative Gynecology, New York, 1900, D. Appleton and Company, vol. 1, p. 466.
17. Lewis, W. H., and Alving, A. S.: Am. J. Physiol. **123**: 501, 1938.
18. Lich, R., Jr.: Surg., Gynec. & Obst. **74**: 475, 1942.
19. Lord, J. W., Jr., and Eckel, J. H.: J. Urol. **48**: 412, 1942.
20. McArthur, L. L.: Surg., Gynec. & Obst. **41**: 719, 1925.
21. McKay, H. W., Baird, H. H., and Justis, H. R.: J. A. M. A. **154**: 202, 1954.
22. Maluf, N. S. R., and Halpert, B.: Surg., Gynec. & Obst. **102**: 27, 1956.
23. Markoe, F. H., and Wood, F. C.: Ann. Surg. **29**: 693, 1899.
24. Poggi, A.: Riforma med. **3**: 314, 320, 1887.
25. Priestley, J. T.: Surg., Gynec. & Obst. **68**: 832, 1939.
26. Schopf, F.: Allg. Wien. med. Zeitung vol. 31, 1887; abstract in Centralbl. Gynäk., No. 30, p. 487, 1887.
27. Shock, N. W.: Geriatrics **1**: 232, 1946.
28. Sisk, I. R.: Trans. Am. A. Genito-Urin. Surgeons **27**: 287, 1934.
29. Sutherland, C. G., Brown, W. E., Atkinson, J. C., and Birmingham, R. T.: South. M. J. **47**: 525, 1954.
30. Tauffer, W.: Ueber einige Fragen der Nieren—und Ureterenchirurgie. Pest. med.-chir. Presse, No. 42, 15 Oct., p. 993, 1893.
31. Van Hook, W.: J. A. M. A. **21**: 911, 1893.
32. Winslow, R.: Ann. Surg. **27**: 46, 1898.

THE RELATIONSHIP OF THE BRENNER TUMOR TO THE RETE OVARII

GRETE STOHR, M.D., NEW YORK, N. Y.

(From the Clinic of the Woman's Hospital)

VARIOUS concepts have been held regarding the nature and histogenesis of the tumor ovarii typus Brenner, as this neoplasm has been called since its first recognition. It was Robert Meyer's[1] constructive histogenetic thinking which rescued this tumor from its misconceived status as a specific form of the granulosa-cell tumor or as a particularly well-differentiated form of the oophoroma.

The pattern of the Brenner tumor consists essentially of foci of glycogen-containing cells with oval or fusiform, frequently medially grooved nuclei, occasionally surrounding a central cavity in such a fashion that the nuclei of the innermost cell layer are situated peripherally from the luminal border of the cell. A darkly staining, protoplasmatic, cell-like body is frequently situated in the central cavity. These cell nests are more or less densely disseminated throughout a coarse, fibrous stroma.

Histogenetic Theories

From these epithelial structures, which give the impression of being maldeveloped or stunted Graafian follicles, the early literature raised the fundamental question as to whether the ovarian follicle was capable of tumor growth and whether the neoplastic development of the egg cell proper was possible.

Tumor Origin From Ovarian Follicle Including Ovum.—The concept of the neoplastic reproduction of the ovarian follicle *including* the ovum was maintained by Emanuel,[2] Acconci,[3] Amann,[4] Gottschalk,[5] Schroeder,[6] and Voigt.[7] They recognized follicles including ova in tumors, in which these structures either represented the formative structure itself or were peculiar attributes of otherwise not unusual neoplasms. The viewpoint of these early writers is explained by their concept of postembryonic egg formation from the follicular epithelium, which was regarded as genetically related to the germinal epithelium, a concept held as late as 1899 by Stoeckel.[8]

Tumor Origin From Ovarian Follicle Without Ovum.—The literature of later date dissented in general from this viewpoint, but accepted the possibility of neoplastic growth of the cell components of the follicle in organoid form.[9-13] Brenner[13] was the first one to describe collected cases in his article entitled "Oophoroma Folliculare." Solely on morphologic grounds he considered the epithelial inclusions as malformed follicles, developed neither from pre-existing follicles nor from Pflüger's cords, as the latter exist only during embryonic life. The entire structure he believed to originate from the germinal epithelium as an organoid development. His position is explained by the then prevalent conception that all tumor formations reproduce in their build, perhaps in faulty form, the structure of their corresponding organ or part of it.

Tumor Origin From Germinal Epithelium.—Lahm[14] and Mandelstamm[15] traced the tumor origin back to elements either derived from or displaced into the germinal epithelium. Thus the latter designated the tumors "blastomata of germinal epithelium (Keimepithelblastome)."

Tumor Origin From Serosa Nodules.—This article preceded by only some months the treatise of Meyer,[1] which stabilized the trend of thought in evaluating the potentialities of the ovarian follicle as an organoid unit. He considered the follicle to be an organoid structure, formed and perfected during embryonic life, highly organized, and as such not capable of reproducing itself by neoplastic processes. He believed likewise that cell elements, which compose this unit in its completed state, are incapable of autonomous proliferation as tumors. Thus, he opposed the concept of the folliculoma in general, but by a comparative histologic and functional analysis he recognized the tumor described by Brenner as an oncologic entity. He called attention to the morphologic similarity of its epithelial inclusions to the epithelial nodes, generally known as Walthard's bodies, although first described by Werth.[16]

Walthard[17] described a variety of congenital cell inclusions of the ovary in adolescents and adults and in women of the postclimacteric phase composed of cells from small, roundish to flat, squamoid form, which may be distributed between the normal surface epithelium, or which may become separated from the surface epithelium and appear at a varying depth in the ovarian stroma. He observed them also beyond the hilus border and in the tubal fimbriae. In the larger foci disintegration of the central cell layers and subsequent cavitation may occur. He considers them as "congenitale Anlagen" accidentally displaced in the ovary, unrelated to the germinal epithelium. He fails to offer any conclusive definition of their histogenesis and rejects an inflammatory etiology.

Walthard's pupil, Akagi,[18] in a study of the heterogenous epithelial inclusions of infants' ovaries, arrived at the same conclusion as Walthard, refuting the inflammatory origin and the capacity of the germinal, that is to say, the surface epithelium of the ovary, to produce squamous epithelium.

Meyer[1] and Heim[19] considered these nests not as congenitally displaced anlagen but as the result of cell differentiation by metaplasia of the celomic mesothelium. The process may be regarded as comparable to the embryonal differentiation of this tissue to produce the multiform epithelial tissues of the Müllerian duct. Meyer considered the celomic epithelium a specific building material, distinct from the mesenchyme and from the parenchymatous complex (Parenchymkern), the male part of the latter including the rete of the testis and of the ovary.

Support is given to the view that the Brenner tumor arises from the celomic epithelium by the fact that the tumor as a primary growth has not been met outside of the ovarian substance or of the hilus, while squamous epithelial nodes develop quite frequently on the serosa of the genital tract, infrequently in the hilus, and very rarely in the ovarian substance. Meyer found them here only twice up to the time of his publication and I have observed them only once in the material of the Woman's Hospital.

Meyer, furthermore, did not accept the cells of the Brenner tumor as true squamous epithelium, but as a primary indifferent cell form which, in the process of differentiation, in analogy with Müller's epithelium, may become stratified. The central cavitation he considers the result of a degenerative process and not the result of cell development. This statement finds support in the observation that the spine cell type was not observed in the numerous histologic analyses of the Brenner tumor in the literature with the exception

of Case 3 of Kleine,[20] who described transition of columnar to pavement epithelium and cornification within one solid epithelial nest of Brenner type situated in the thickened wall of a seroepithelial cyst. From the corresponding illustration, No. 6, however, a definite clear impression cannot be obtained.

Different explanations of the serosal epithelial nodes were offered by Schickele[21] and Pick[22]; the latter considered them as newly formed, juvenile adrenal gland tissue developed from the peritoneal epithelium.

Plaut[23] described eight cases of Brenner tumor and discussed its histogenesis. He supported Meyer's theory, for which he considered his case No. 8 definite histologic proof, as he regarded the squamoid-cell nodules products of postembryonic proliferative processes of the peritoneal tissues.

Tumor Origin From Rete Ovarii.—A profoundly new viewpoint of the histogenetic background of the Brenner tumor was gained by Schiller[24] in a study of collected cases. One of them, No. 4, presented a neoplasm of microscopic size in connection with the epoophoron and with rete tubules, in which the transition of the epithelium of these vestigial tissues into the typical Brenner epithelium could be demonstrated. By a detailed analysis of the embryonic relationship of the mesonephros and of the ovarian rete he derived the Brenner tumor from rudiments of these embryonic structures. He considered the epithelial tissue of the Brenner tumor the result of identical differentiation of these two organs, the mesonephros and the rete ovarii, on the basis of their common genetic background and of their temporary union during embryonic life. He traced their origin from the primary mesenchyme of the urogenital ridge and of the rete blastema. He thereby accepted the unitarian concept, which regards the mesenchyme of the urogenital fold as the common source of the celomic epithelium, of the parenchymatous nucleus of the gonad (Epithelkern), and of the mesonephros. This was the view postulated by Fischel,[25] who considered the ovarian rete the residue of the primary sex cords, which temporarily unite with the mesonephros in female embryos of 6 cm. length, to be disconnected again at the end of embryonic life.

Meyer[1] and Kleine,[20] on the other hand, believed in a strict separation between the mesenchyme, the celomic epithelium, and the internal epithelial mass (Epithelkern) in regard to their potentialities of differentiation and considered the heterosexual complex with its intrinsic internal secretory properties part of the internal epithelial mass. They rejected the probability that the Brenner tumor develops from the rete as a derivative of the heterosexual complex, as it lacks internal secretory function, which is expected of tumors derived from these sexually oriented tissues.

Histogenesis of the Rete Ovarii.—The histogenesis of the ovarian rete and consequently the evaluation of its vestigial tissues have not been agreed upon, nor has the concept of the temporary union of the gonadal and the mesonephric systems, i.e., the union of the sex cords with the epigenital portion of the mesonephros by means of the medullary cords (rete blastema) been fully accepted. In regard to this, Clara[26] in his textbook of embryology writes: "Somewhat later than in the male appear also in the female gonad in the zone neighboring the mesovarium, separated from the sex cords, the medullary cords; in contrast to the male gonad, they do not unite directly with the egg nests (Eiballen) nor with the mesonephric tubules."

The histogenesis of the ovarian rete was the subject of many investigations, carried out on animal and human material. Spuler[27] has presented a review of these investigations, which after originally varied results produced ultimately a clear concept as to the basic genetic processes. The early investigations[28, 29] maintained the derivation of the rete blastema from the celomic mesothelium, which in the form of cords embed themselves between the sex cords and the

mesonephric glomeruli, subsequently entering anastomoses with Bowman's capsules. Michalkovits,[30] Sainmont,[31] Sainmont and Winiwarter,[32] and Winiwarter,[33] working with human material, demonstrated the origin of the rete from Bowman's capsules of the regio epigenitalis of the mesonephros.

Results of investigations conducted by Felix[34] and Wichman[35] on human beings and on animals refute entirely the connection of the rete with derivatives of the mesonephros. The primary building material of the rete blastema derives from the mesothelium of the genital ridge, entering the mesenchyma with the former on its primary downgrowth, where it remains as a compact cell mass in undifferentiated state for a long time. Later the blind ends of the tubuli collectivi will be surrounded by the epithelial mass in such a fashion that the ends of the tubuli become situated back to back with the rete blastema, whereby the false impression of their genetic correlation is produced.

Thus, the origin of the rete has been demonstrated as independent from the mesonephric system, but is traced to the celomic mesothelium of the genital ridge or from the mesenchymal tissue in its undifferentiated state. The final decision, which of these two sources is to be accepted, hinges on the two opposite trends of thought, namely, to include the celomic mesothelium in the mesenchymal tissue (Fischel, Schiller), or to separate it as a histologic and formative unit of the tissues pertaining to the urogenital ridge. Either histogenetic evaluation of these tissues will lend itself as an equally valid background for the correlation between the serosa nodules (Werth, Walthard) and the rete ovarii and, therefore, both structures may serve as histogenetic source for any tissue or neoplastic growth, representing the result of their cell differentiation and cell proliferation. Considering the Brenner tumor as such, its correlation with the rete may find support in some clinical observations. The rete in its rudimentary form in the adult female reaches a new height of growth, exactly when the incretory activity of the gonad is on its decline and at this period of life the Brenner tumor will be most frequently found.

The more recent literature has added to the probability of origin of this tumor from the rete. Fauvet[36] described several cases of Brenner tumor and discussed its histogenesis. Case 1 in Fauvet's series concerned one of two small tumors in the same ovary. The smaller tumor included in the portion facing the rete a flat, tortuous tubule without stratification, which he believed to be rightly designated a rete tubule. In Fauvet's Case 4 a Brenner nodule was situated in the vascular zone of the ovary in close proximity to the rete. Serial sections disclosed a direct connection with the rete, several ducts of which presented epithelial stratification and solid epithelial inclusions. Fauvet referred to Walthard's and Meyer's statements, that the potency of cell differentiation of the serosal nodules depends upon a healthy connective tissue stroma. Assuming a common histogenetic background he considered the epithelial nodules and the rete equally available for transformation into the characteristic Brenner tumor epithelium.

Kleitsman[37] described one case of Brenner tumor, surveying the literature exhaustively and discussing the various viewpoints as to its origin. He was willing to accept any of the aforementioned theories on the basis of a common mesodermal origin of the tissues involved.

Reagan[38] reported on 23 cases, 2 of which were studied by serial sections. A small subcortical tumor showed definite continuity with superficial inclusions, morphologically identical with Walthard's cell nests.

Kerpe and associates[39] described a case of simultaneous development of squamoid epithelial structures in the endometrium and in one ovary. The specimen, first obtained by curettage, was diagnosed as adenoacanthoma of the endometrium, but after the findings in the ovary was considered a Brenner tumor and offered as proof of the origin of this tumor from Müllerian

epithelium. Doubt may be raised, however, as to the validity of the revised diagnosis in view of the not infrequent squamous cell metaplasia of malignant epithelial tumors of the ovary.

Greene,[40] in a study of 18 cases, considered four sources and modes of development: (1) from the rete ovarii; (2) as the result of metaplasia of the ovarian stroma; (3) from the ovarian surface epithelium; (4) from a pseudomucinous cystadenoma (as conceived by Meyer as part of a teratoma). In seven of his 14 cases of frank Brenner tumor he suggested relationship between the epithelium and rete cords. His classification depends on morphologic criteria of the epithelial inclusions and in the case of source 2 on the presence of reticulum fibers in the tumor stroma.

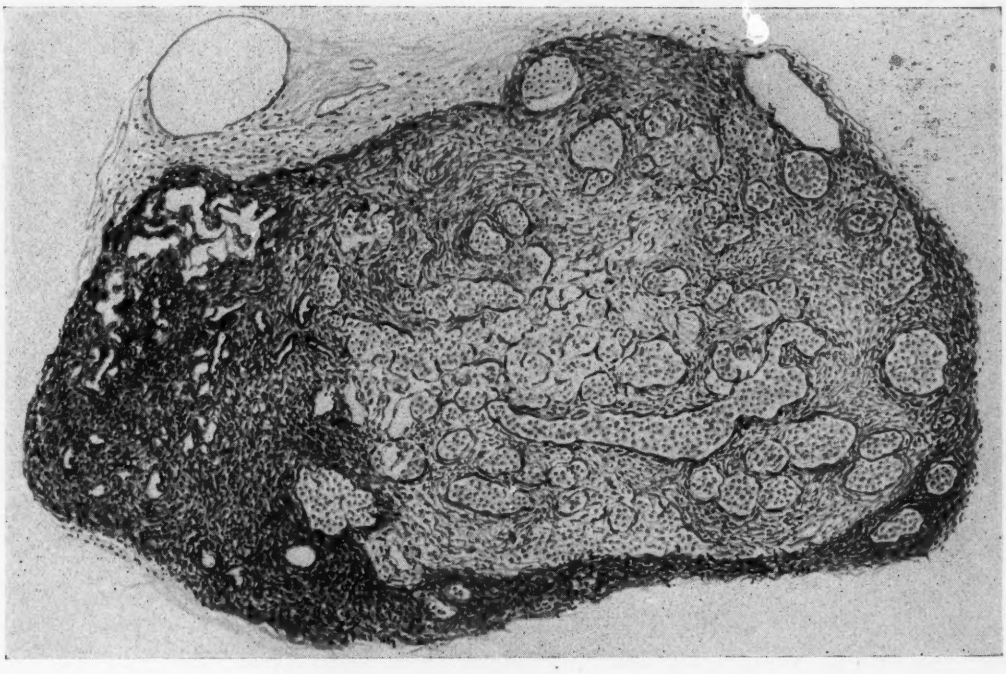


Fig. 1*A*.—Case 1. Tumor and rete ovarii.

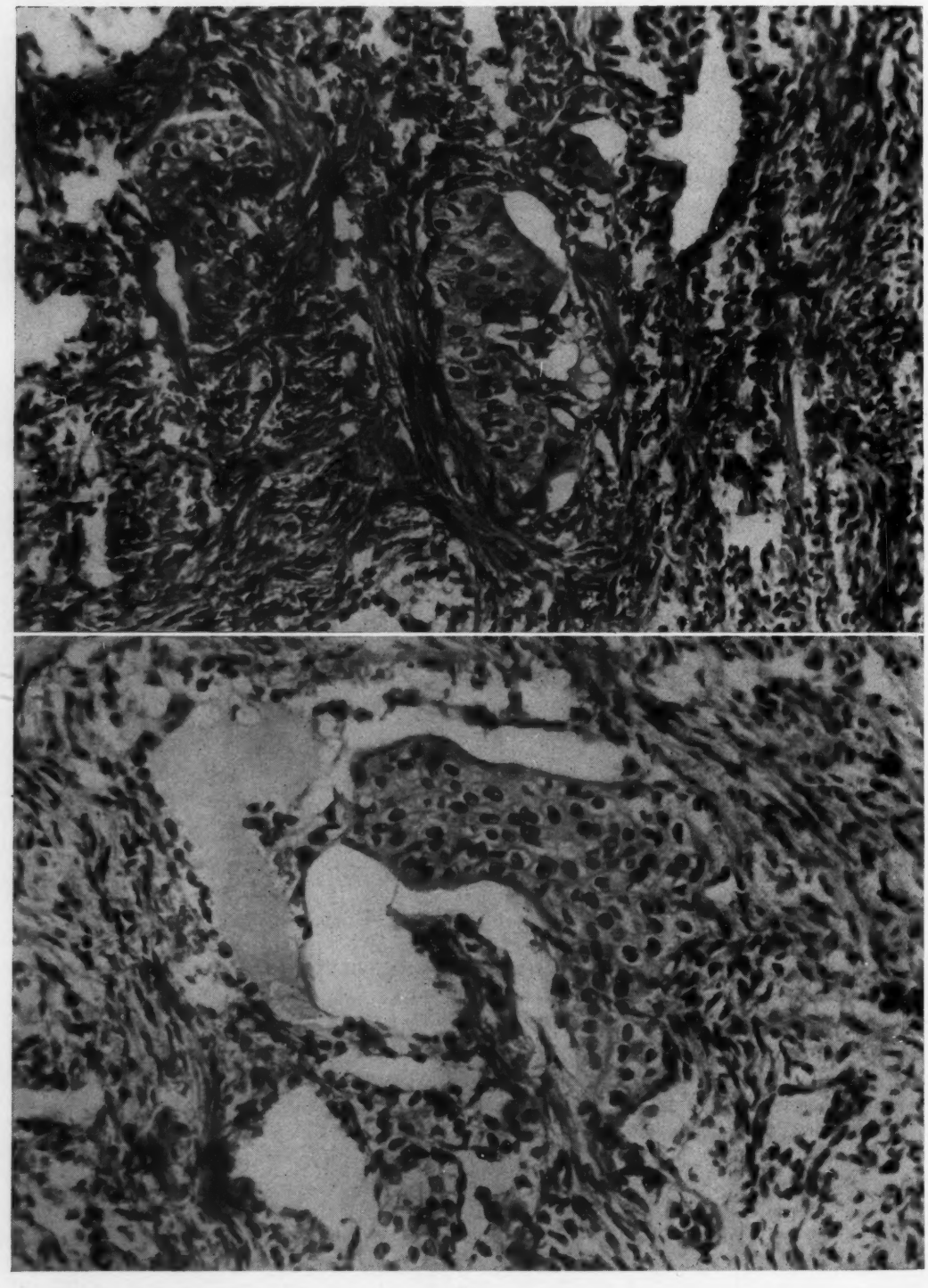
Case Reports

The following cases are presented to support the evidence of the genetic correlation of the rete ovarii and the Brenner tumor.

Case 1.—Patient I. P., aged 41 years, was operated upon at the Woman's Hospital (P.N. 51151) for pelvic adhesions following eight years after resection of the right uterine appendages and appendicectomy. At operation a small uterus was found buried in dense adhesions to omentum, sigmoid, and rectum, involving the left appendages. The ovary included few small follicular cysts and a corpus luteum.

Microscopic Findings.—The ovary was studied by interrupted series along the anteroposterior axis, starting from the midfrontal plane. An unusually large rete was found situated close to the superior margin in the region of the hilus, but outside of the vascular zone of the ovary. Separated from the latter by a layer of unspecific, parvicellular connective tissue was an adjacent Brenner tumor (Fig. 1*A*). A circular layer of smooth muscle fibers supported the frame of the tumor. The rete tubules were more densely distributed at the margin of the rete than throughout the central and medial portion, where the stroma was more abundant. The lumina of the peripheral tubules were widely distended, while the central and medial tubules were narrower and less sinuous, some being reduced to

B.



C.

Fig. 1.—*B*, Detail of Fig. 1*A*. Transition from columnar to squamoid epithelium. *C*, Detail of Fig. 1*A*. Intraluminal, papilliform proliferation of squamoid epithelium.

irregular clefts. The tubules were either separated from each other by thin stromal septa, or, more frequently, they anastomosed. The luminal surfaces varied considerably due to the formation of intraluminal folds in the wider tubules, which locally formed secondary branchings. The lining, which was a serous epithelium supported by a basement membrane, showed morphologic variation, as it presented all gradations from the low cuboidal to the medium tall columnar form, yet retained throughout the essential characteristics. The cuboidal type prevailed in the most medial tubules, while in some closer to the Brenner tumor a transition from the seroepithelial to a stratified squamoid type had occurred (Fig. 1*B*). This process appeared partly as a very gradual metaplastic transformation, partly as an abrupt change, in such a fashion that the lumen was lined in one part by a flat cuboidal epithelium and by the squamoid type in the other part; or the epithelium in the lumen of one tubule bulged in polypoid fashion into a neighboring tubule (Fig. 1*C*). Where local stratification of the squamoid epithelium had occurred, papilliform projections were produced, giving the impression of a neoplastic growth, which exhibited by cell form, shape

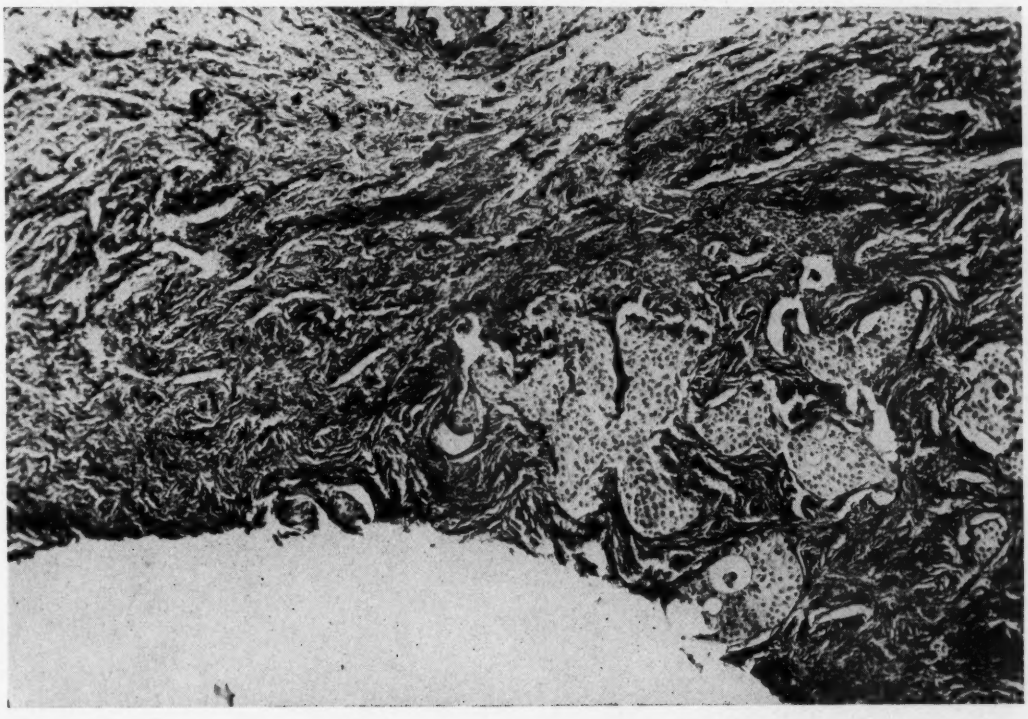
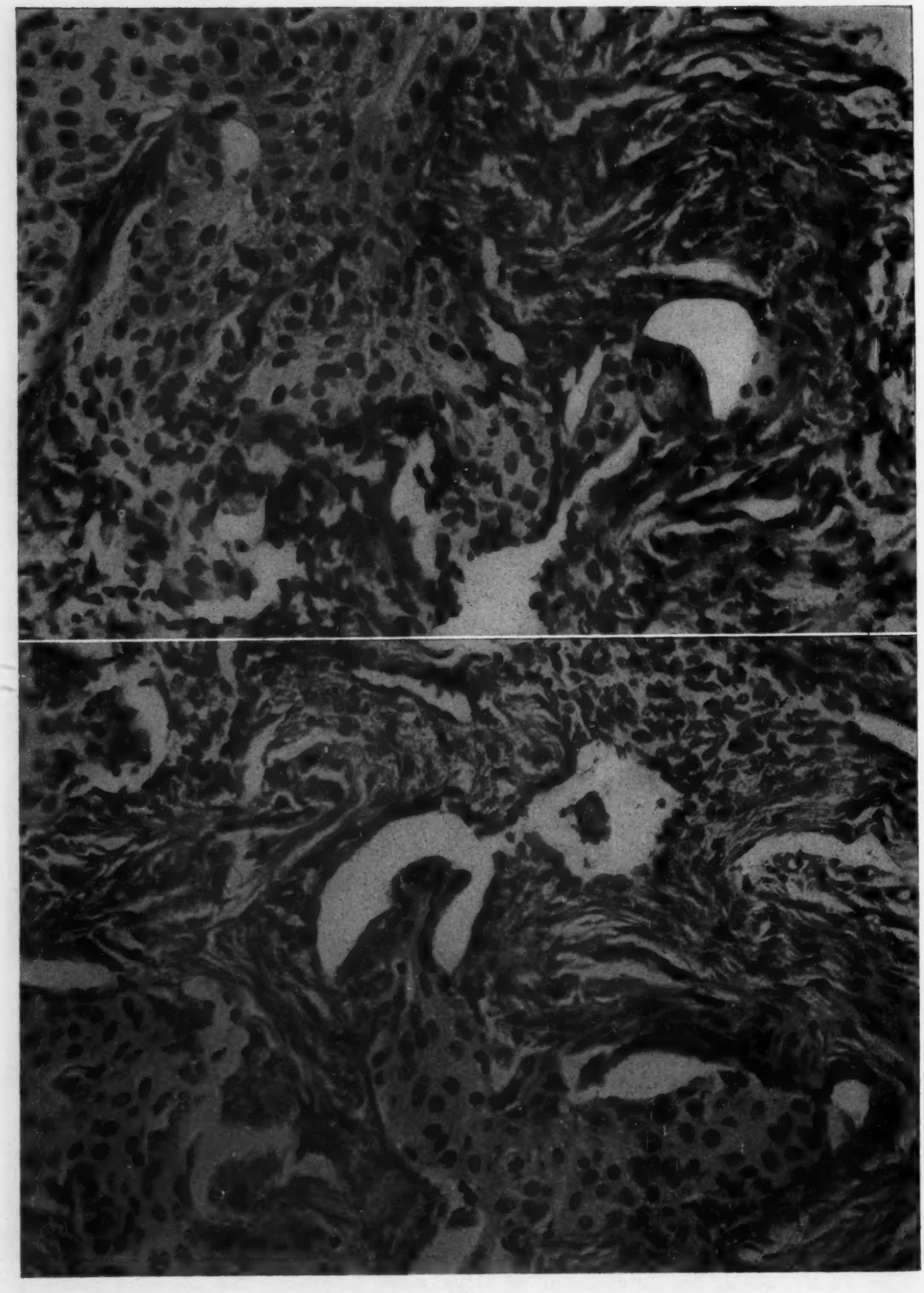


Fig. 2*A*.—Case 2. Rete tubules connecting with squamoid cell inclusions of Brenner tumor.

and texture of nuclei, and by the orientation of cells the criteria of the epithelial structures of the Brenner tumor. This impression was supported by the direct merging of the epithelial inclusions of the tumor proper with rete tubules, overgrown by squamous-cell epithelium. On the other hand, some of the Brenner inclusions, which were closest to the rete, were supported by a basement cell layer, which still bore the appearance of compressed rete epithelium. The largest epithelial inclusion had the unusual shape of a long strand, which branched at one extremity and terminated in the form of alveolar bulbs. As the epithelium had locally retracted from its stroma base, the impression of a duct lumen was obtained, being obliterated by the proliferating epithelium.

Case 2.—Mrs. O. C., aged 44 years, was operated upon at Booth Memorial Hospital, New York (R.N. 32096), for metrorrhagia of three years' duration. The operative specimen consisted of a myomatous uterus and its left appendages. The ovary, 4 by 2.6 by 1.6 cm. in its largest dimensions, was sectioned along its mesolateral axis, dividing it into approximately equal halves, one of which presented the hilus region and the adjacent portion of

B.



C.

Fig. 2.—*B*, Detail of Fig. 2*A*. Complete or partial effacement of rete tubules by proliferated squamoid epithelium. *C*, Detail of Fig. 2*A*. Indenting of squamoid epithelium into rete tubules.

Fig. 3.—Case 3. Rete tubules connecting with squamoid epithelial nodule.

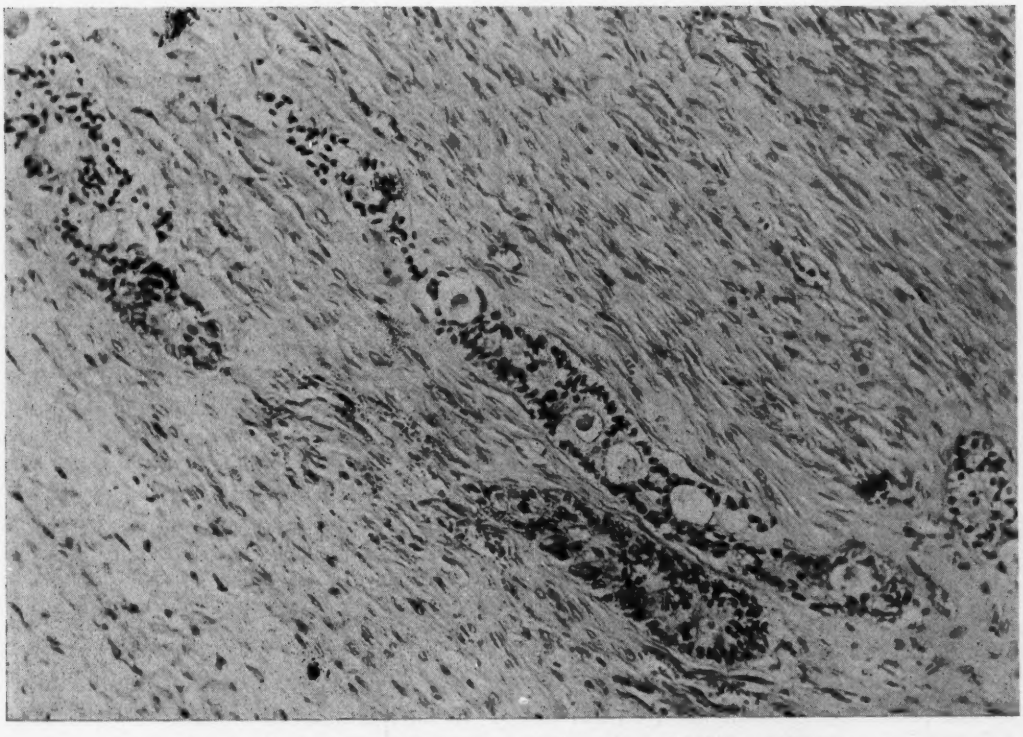


Fig. 4.—Case 4. Tubular form of Brenner epithelium inclusion.

the mesovarium. A well-developed rete was found situated at the hilus border in such a position that a smaller portion extended into the tissues of the mesovarium. Besides the main mass of the rete, widely spaced individual tubules were scattered along the lower border of the section. Interpolated between the tubules of the extraovarian portion was a group of cell nests, which bore all the morphologic characteristics of the epithelial inclusions of the Brenner tumor (Fig. 2*A*). The rete tubules were narrow, frequently reduced to clefts, sinuous, and so intimately anastomosed that their individual course could not be clearly outlined. Their lining was mainly a flat, simple, epithelial layer, cells of which were situated parallel to the luminal surface in endothelial fashion; only in a few instances were the cells of low cuboidal type. The tubules of the ovarian border area were widely distended to bizarre formations and were occupied by a stratified squamoid epithelium, which by proliferation had led locally to complete effacement of the rete tubule (Fig. 2*B*). In other places the squamoid epithelium developed in the lumen of one tubule indented into the lumen of a neighboring tubule by penetration of the wall (Fig. 2*C*). While in many of the tubules a transition from a flat, endothelium-like type to the cuboidal and finally to the squamoid type was apparent, the character of an independent growth was developed, where complete obliteration of the rete epithelium had occurred. Central necrosis of the compact cell nests with accumulation of debris in the cavities produced the familiar picture of pseudofollicles. Most of the cell nests were surrounded by a frame of acellular collagenous substance, but in some places an imperceptible merging of epithelium and stroma was apparent, which, as demonstrated by Masson's trichrome stain, showed texture and tinctorial quality identical with those of the specific ovarian stroma. A walling off of the Brenner cell nests by an individual capsule was absent.

CASE 3.—Another incidental finding in a surgical specimen, obtained from the Manhattan General Hospital, New York (P.N. 1348), may demonstrate a very initial state of Brenner tumor-rete relationship. In an ovary with a pedunculated follicular cyst, but otherwise of natural structure, the rete of usual appearance was found in close proximity to two solid squamoid epithelial nodes, which were situated at the root of the tuboovarian ligament (Fig. 3). The intervening stroma was occupied by several discrete, narrow rete tubules in linear distribution, linking the epithelial nodes to a large papillary rete tubule, like the two poles of an imaginary junction. Moreover, the epithelial lining of one of the intervening tubules showed low-grade cell hypertrophy, radial arrangement, and inclusion of cell debris, approaching the appearance of a stunted primordial follicle, a structure similar to those frequently appearing in the Brenner tumor.

CASE 4.—Though morphologic likeness of histologic structures is of minor importance as a documentary criterion for a common histogenetic background, a case from the material of the Department of Surgical Pathology, College of Physicians and Surgeons (No. 21345), will give appreciable support to the preceding presentation (Fig. 4). The gross specimen was a large ovarian tumor, which replaced the ovary completely. Microscopic examination of sections from different parts showed a rather dense dissemination of epithelial structures throughout a fibrous stroma. These formations were predominantly slender tubules, which showed intraluminal glandular budding, possibly the visual effect of tortuosity. The tubules and their rosette-shaped inclusions bore an epithelium which varies from a flat, endothelium-like to low columnar type, producing a mucicarmine-positive secretion. The tumor was diagnosed as a Brenner tumor, corresponding to its histologic structure.

Most striking in this case was the tubular pattern, which might well have been carried over from the anlagen as a primary tubular structure. In the case published by Freund[33] a similar histologic pattern was described in one of the cases.

Résumé

A review of the various theories of origin of the tumor typus Brenner has been presented, from its primary concept as a specific type of the oophoroma, to its final recognition as a tumor *sui generis*, independent from the ovarian follicle.

Two theories of its histogenesis have been discussed, namely, the origin from the serosa nodules and the origin from the rete ovarii.

After evaluation of both possibilities, the tumor is considered a connecting link between these topographically, morphologically, and biologically disconnected structures. On the basis of these considerations the tumor is to be regarded as the result of cell differentiation and neoplastic cell proliferation of either one of these tissues.

Four cases have been offered in support of the validity of the concept, correlating the Brenner tumor with the rete ovarii.

Hereby I wish to express my appreciation to Dr. Arthur P. Stout, Professor Emeritus of Surgery, Columbia University, for his helpful suggestions on reviewing this article and for the permission to include a case of the material of the College of Physicians and Surgeons, New York.

References

1. Meyer, R.: Arch. Gynäk. **148**: 541, 1932.
2. Emanuel, R.: Ztschr. Geburtsh. u. Gynäk. **3**: 187, 1892.
3. Acconci, L.: Zentralbl. allg. Path. u. path. Anat. **1**: 738, 1890.
4. Amann, J. A.: Zentralbl. Gynäk. **24**: 1287, 1896.
5. Gottschalk, S.: Arch. Gynäk. **59**: 676, 1899.
6. Schroeder, R.: Arch. Gynäk. **64**: 193, 1901.
7. Voigt, M.: Arch. Gynäk. **70**: 86, 1903.
8. Stoeckel, W.: Arch. mikr. Anat. **53**: 357, 1899.
9. von Mengershausen, J.: Inauguraldissertation, Freiburg, 1894.
10. von Kahlden, C.: Zentralbl. allg. Path. u. path. Anat. **6**: 7, 1895.
11. Orthman, E. G.: Monatsschr. f. Geburtsh. **9**: 777, 1899.
12. Lonnberg, I.: Nord. med. Ark. aft. 1, 34:1, No. 17:1, 1901.
13. Brenner, F.: Frankfurt. Ztschr. Path. **1**: 180, 1907.
14. Lahm, W.: Beitr. Geburtsh. u. Gynäk. **19**: 261, 1913-1914.
15. Mandelstamm, A.: Arch. Gynäk. **148**: 494, 1932.
16. Werth, R.: Beitr. Anat. u. z. operat. Behandlung d. Extrauteringrav., Stuttgart, 1887, p. 110.
17. Walthard, M.: Ztschr. Geburtsh. u. Gynäk. **49**: 233, 1903.
18. Akagi, Y.: Arch. Gynäk. **134**: 390, 1928.
19. Heim, K.: Berichte ü d. ges. Gynäk. u. Geburtsh. **17**: 641, 1930.
20. Kleine, H. O.: Ztschr. Geburtsh. u. Gynäk. **114**: 125, 1937.
21. Schickele, G.: Virchows Arch. path. Anat. **169**: 183, 1902.
22. Pick, L.: Arch. Gynäk. **64**: 670, 1901.
23. Plaut, A.: Arch. Gynäk. **153**: 97, 1933.
24. Schiller, W.: Arch. Gynäk. **157**: 65, 1934.
25. Fischel, M.: Die Entwicklung des Menschen, Vienna u. Berlin, 1929, Julius Springer, p. 617.
26. Clara, M.: Entwicklungsgeschichte des Menschen, Leipzig, 1938, Quelle & Meyer, p. 343.
27. Spuler, A.: In Veit-Stoeckel: Handbuch der Gynäkologie, Munich, 1938, Bergmann, vol. 1, sect. 1, p. 423.
28. Coert: Dissertation, University Leyden, 1898.
29. Allen, M. B.: Am. J. Anat. **5**: 79, 1905.
30. von Michalkovits, G. V.: Internat. Monatsschr. Anat. u. Histol. **2**: 41, 1885.
31. Sainmont, G.: Arch. de biol. **22**: 71, 1905.
32. Sainmont, G., and von Winiwarter, H.: Arch. de biol. **24**: 1, 1908-1909.
33. von Winiwarter, H.: Arch. de biol. **25**: 683, 1910-1911.
34. Felix, W.: Handbuch der Entwicklungsgeschichte des Menschen, Leipzig, 1911, Keibel and Mall, S. Hirzel, vol. 2, p. 732.
35. Wichman, S. E.: Anat. Hefte **14**: 629, 1911-1912.
36. Fauvet, E.: Arch. Gynäk. **159**: 585, 1935.
37. Kleitsman, R.: Acta obst. et gynec. scandinav. **27**: 33, 1947.
38. Reagan, J. W.: Am. J. Obst. & Gynec. **60**: 1315, 1950.
39. Kerpe, S., Black, M. M., and Speer, F. D.: A. M. A. Arch. Path. **54**: 139, 1952.
40. Greene, R. R.: Am. J. Obst. & Gynec. **64**: 878, 1952.
41. Freund, R.: Arch. Gynäk. **155**: 67, 1933.

10 West 74th Street

GLYCOGEN IN INVASIVE SQUAMOUS CARCINOMA OF THE UTERINE CERVIX*†

ALVAN G. FORAKER, M.D., AND GENEVIEVE MARINO, JACKSONVILLE, FLA.

(From the Pathology Laboratory, Baptist Memorial Hospital)

ABSENCE of glycogen in squamous carcinoma of the uterine cervix is almost axiomatic in gynecological pathology.[1, 2] Schiller[2] indicates that the faculty of glycogen storage is absent in carcinomatous epithelium. This has led to the well-known Schiller test. McManus and Findley[3] demonstrated absence of glycogen in the hyperactive epithelium of eight cases of carcinoma in situ of the cervix. Ayre and Ayre[4] suggested that the glycogen staining reaction offered a means of correctly identifying nonneoplastic squamous cells of unusual morphology in cervical or vaginal smears.

Two studies in our laboratory in recent years have suggested that glycogen may be present in squamous carcinoma of the cervix. Denham and Foraker[5] found a glycogen staining reaction in maturing tumor cells in a case of squamous carcinoma of Bartholin's gland. Glycogen was demonstrated in well-differentiated tumor cells[6] in a histochemical study of thirty-eight cases of squamous carcinoma from bronchus, penis, vulva, skin, oral mucosa, maxillary sinus, and metastatic in lymph nodes. These studies prompted an investigation into the glycogen staining reaction of 21 examples of invasive squamous carcinoma of the uterine cervix. Thirteen of these showed some glycogen reaction of the carcinoma cells.

Materials and Methods

Biopsies of 21 examples of invasive squamous carcinoma of the cervix were fixed in ice-cold alcohol. After paraffin embedding, sections (5 μ) were subjected to the periodic acid-Schiff technique for the demonstration of glycogen.[7] Control sections were digested with 0.1 per cent malt diastase for 30 minutes to remove glycogen. All sections were counterstained with hematoxylin.

Results

Thirteen of the 21 cases showed some degree of glycogen staining in the cytoplasm of some of the carcinoma cells. In examples of well-differentiated carcinoma, the glycogen staining was more marked toward the centers of the neoplastic masses, where there was evidence of maturation of the cells. Occasionally, however, some diffusely growing tumors manifested slight degrees of glycogen staining (Figs. 2 and 3). In the control sections subjected to malt diastase digestion (Fig. 1, *B*), no glycogen type staining was seen and there was no periodic acid-Schiff positive material in the cytoplasm of the tumor cells. A moderate amount of fibrous tissue staining was present in test and control

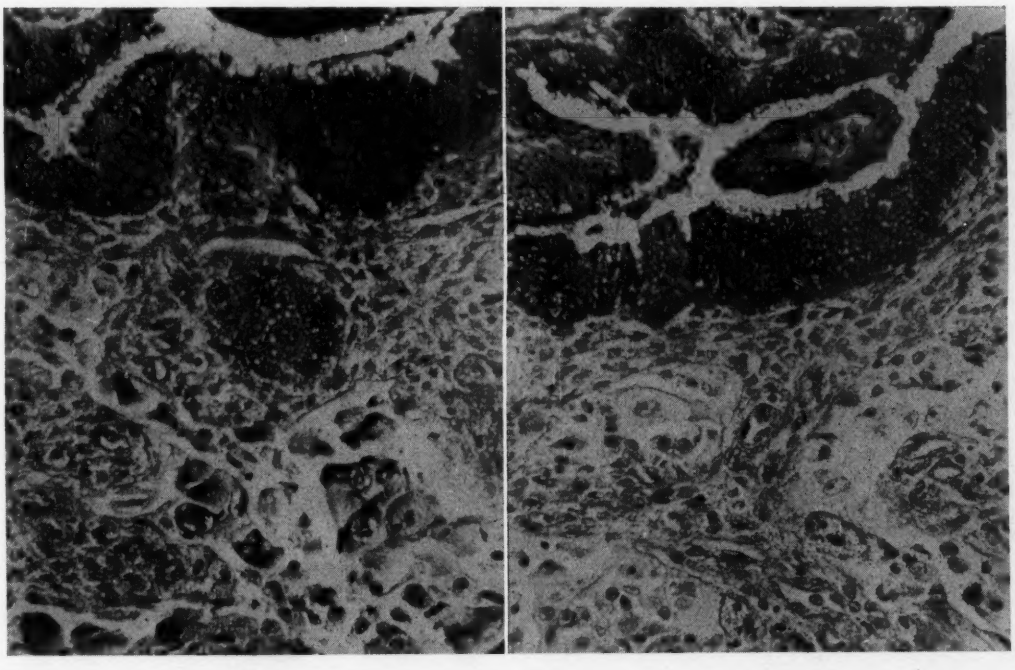
*Portions of this work were done in the Department of Pathology, University of Texas, M. D. Anderson Hospital and Tumor Institute, Houston, Texas.

†This investigation was aided by Research Grants C-2111 and C-2392 from the National Cancer Institute, National Institutes of Health, U. S. Public Health Service.

sections. Mucus in endocervical glands (Fig. 1, *A* and *B*) stained with equal intensity in test and control sections, being unaffected by malt diastase digestion. A few leukocytes showed weak glycogen type staining.

Comment

Three variables probably contribute in some degree to the complexity of this problem: the nature of glycogen, variations in fixation, and variations in staining technique. Glycogen is not a pure chemical substance. There are a number of different glycogens of varying degrees of polymerization,[8] all composed of D-glucose units. These glycogens have different solubilities. Various fixatives have been used in glycogen studies. For some time it was believed that considerable amounts of glycogen were lost in aqueous solutions such as formalin. Alcohol and various alcoholic fixatives such as Rossman's fluid[7] were widely used. Lillie[7] states that neutral aqueous formalin solutions often preserve



A. *B.*

Fig. 1.—*A*, Squamous carcinoma of the cervix (periodic acid-Schiff technique, hematoxylin counterstain). Endocervical gland in upper part of field contains strongly staining mucin. Squamous carcinoma cells in lower part of field reveal moderate glycogen reaction in the cytoplasm (×342; reduced 2/7.)

B, Squamous carcinoma of the cervix (periodic acid-Schiff technique, hematoxylin counterstain, malt diastase digested). Section from same block as in *A*, but subjected to malt diastase digestion to remove glycogen. Mucin staining of endocervical glands is unaffected. Schiff positive material has been removed from squamous carcinoma cells in lower part of field. The identity of this substance as glycogen is proved. (×342; reduced 2/7.)

glycogen quite well, but certain acid alcoholic fluids seem prompter and more reliable. In their study of intraepithelial carcinoma, McManus and Findley[3] used formalin fixation. Ayre and Ayre[4] fixed their smears in 95 per cent alcohol for glycogen staining. We used ice-cold alcohol, since we wished to do alkaline phosphatase and phosphamidase[8, 9] studies on the same blocks. Some of the comparative studies of fixation and glycogen preservation[7] have been done on

glycogen-rich tissues such as rat liver. A considerable amount of glycogen may have been lost from these during fixation with little effect on the staining reaction. When dealing with admittedly glycopenic cells such as those of squamous carcinoma, perhaps the method most likely to preserve the maximum amount of glycogen should be employed.

There are five basic methods in use for the demonstration of glycogen, and all have some merit.[8] McManus[3] and Lillie[7] prefer the periodic acid-Schiff technique, which we used. Pearse[8] suggests Best's carmine for routine use. This was employed in Ayre and Ayre's[4] cytological studies. Silver, iodine, and Bauer-Feulgen techniques probably have no advantage.[8] Standard texts on histochemistry[7, 8, 9] agree that whichever method is used for demonstrating glycogen, control sections must also be used. These are incubated in saliva, or preferably in malt diastase. Material which resists diastase digestion is not glycogen,[8] and is probably some more complex carbohydrate, such as a mucopolysaccharide.

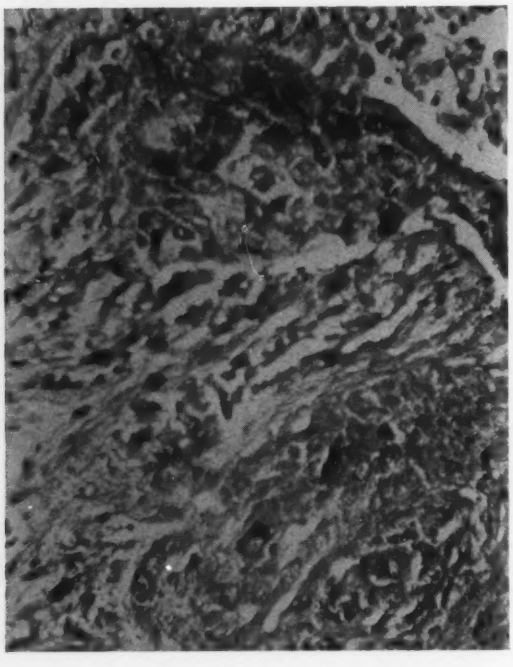


Fig. 2.

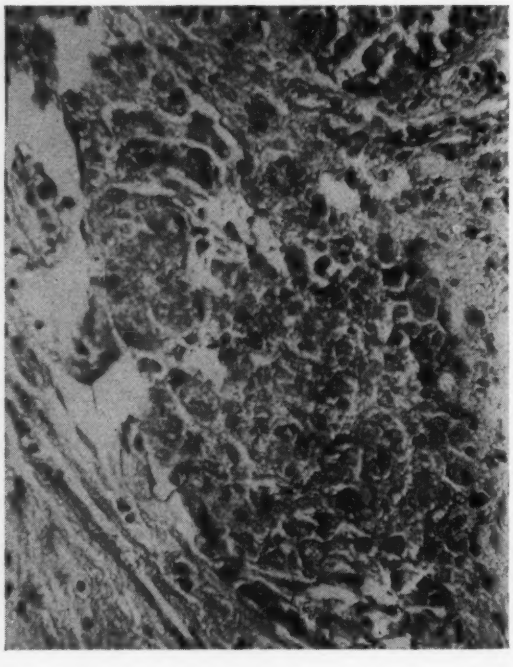


Fig. 3.

Fig. 2.—Squamous carcinoma of the cervix (periodic acid-Schiff technique, hematoxylin counterstain). Moderate glycogen stain is seen in diffusely growing tumor cells. (×342; reduced ⅔.)

Fig. 3.—Squamous carcinoma of the cervix (periodic acid-Schiff technique, hematoxylin counterstain). Moderate glycogen staining is seen in the cytoplasm of cells of a rather small cell type of squamous carcinoma of the cervix. (×342; reduced ⅔.)

Ayre and Ayre[4] do not mention enzyme digestion control in their cytological investigation. However, we have not seen significant diastase-resistant periodic acid-Schiff positive material in squamous cells, whether from normal or neoplastic cervix, other mucosa, or from skin. Therefore we have no reason to feel that the Best's carmine positive material in Ayre and Ayre's cervical and vaginal smears was not glycogen.

Admittedly there is less glycogen staining material in carcinoma than in normal epithelium of the portio vaginalis. Even in normal squamous mucosa, however, cells from the basal layer contain little glycogen. Glycogen in squamous mucosa of the female genital tract is associated with maturation.[10] Cells of the differentiated basal type in smears are most difficult to classify[4] and these rarely contain glycogen in tissue sections. Most of the cells in smears have desquamated or been scraped from an epithelial surface, whatever their cell type. Since squamous carcinoma cells may contain some glycogen in tissue sections, presumably it is possible for them to do so in smears. Therefore it might be hazardous to rely on presence or absence of glycogen staining as the deciding criterion in designating a problem squamous cell as benign or carcinomatous.

Our present study, unfortunately, includes no examples of intraepithelial carcinoma. On occasion we have been able to demonstrate faint glycogen staining in certain sections of intraepithelial carcinoma. It is our impression that glycogen staining in general diminishes from normal mucosa to metaplasia to dysplasia to intraepithelial carcinoma to invasive carcinoma. No doubt many individual exceptions to this exist.

After reviewing a battery of histochemical techniques (including glycogen) applied to a variety of examples of squamous carcinoma of noncervical origin, it appeared[6] that cytochemical evidence of differentiation paralleled cytomorphological evidence of differentiation. None of the histochemical techniques promised to be of practical assistance in a sharp demarcation between neoplastic and nonneoplastic patterns of squamous epithelium. The present study suggests that this lack of sharp demarcating quality applies also to glycogen in the problem of cervical carcinoma. The absence of glycogen staining cannot be a sine qua non in the diagnosis of squamous carcinoma of the uterine cervix.

Summary

Variable degrees of glycogen staining were demonstrated in 13 of 21 examples of invasive squamous-cell carcinoma of the uterine cervix. Caution in interpreting the absence or presence of glycogen staining as a highly valid criterion in the diagnosis of cervical carcinoma in smears or tissue sections is advised.

References

1. Novak, E.: Gynecological and Obstetrical Pathology, ed. 2, Philadelphia, 1947, W. B. Saunders Company.
2. Schiller, W.: In Anderson, W. A. D., editor: Textbook of Pathology, ed. 2, St. Louis, 1953, The C. V. Mosby Company.
3. McManus, J. F. A., and Findley, L.: Surg., Gynec. & Obst. **89**: 616, 1949.
4. Ayre, W. B., and Ayre, J. E.: Am. J. Clin. Path. **20**: 644, 1950.
5. Denham, S. W., and Foraker, A. G.: Am. J. Obst. & Gynec. **67**: 1151, 1954.
6. Foraker, A. G.: Histochemical Studies in Squamous Carcinoma, Cancer **9**: 367, 1956.
7. Lillie, R. D.: Histopathologic Technic and Practical Histochemistry, ed. 2, New York, 1954, The Blakiston Company, Inc.
8. Pearse, A. G. E.: Histochemistry, Theoretical and Applied, Boston, 1953, Little, Brown & Co.
9. Gomori, G.: Microscopic Histochemistry, Chicago, 1952, The University of Chicago Press.
10. Papanicolaou, G. N., Traut, H. F., and Marchetti, A.: The Epithelia of Women's Reproductive Organs, New York, 1948, The Commonwealth Fund.

CONGENITAL ADRENAL HYPERPLASIA (PSEUDOHERMAPHRODITISM) BEFORE AND AFTER CORTISONE THERAPY

I. Adolescent Development and Menstruation

ELIZABETH KNAPP SMITH, PH.D., AND RUSSELL R. DE ALVAREZ, M.D., SEATTLE, WASH.

(From the Department of Obstetrics and Gynecology, University of Washington School of Medicine)

CONGENITAL adrenal hyperplasia causes pseudohermaphroditism when the adrenocortical hyperplasia appears during the third to the fifth month of intrauterine embryonic development. Adrenal virilism or the adrenogenital syndrome results when the hyperplasia of the adrenal cortex appears later in extrauterine life. From the clinical standpoint, the congenital adrenal hyperplasia syndrome is characterized by accelerated growth during childhood, excessive muscular development, early growth of sexual hair, early epiphyseal ossification, and progressive virilization. Typical symptoms of the syndrome which provoke medical consultation by the adolescent girl or young woman are amenorrhea, lack of breast development, and hirsutism. All these symptoms are attributed to excessive secretion of androgens by the adrenal cortex.

Congenital adrenal hyperplasia is distinct from another form of hyperadrenocorticism, Cushing's syndrome, in which almost all symptoms result from excessive secretion of glucogenic corticosteroids by the adrenal cortex rather than from adrenal hypersecretion of androgens. The excessive secretion of these glucocorticoids may be caused by a tumor in the adrenal or by adrenal hyperplasia, either primary in the adrenal or secondary to a pituitary lesion.

Until very recently, there was no satisfactory treatment for patients with congenital adrenal hyperplasia. In 1950 Wilkins[1] demonstrated the remarkable response to and the effectiveness of cortisone in suppressing adrenal androgen secretion, thus permitting feminization to occur. These results have since been confirmed by others.[2, 3, 4] As a consequence of these findings, increased interest has developed in determining the fundamental biochemical metabolic defect causing the syndrome.

Typical findings in the untreated patient include markedly elevated urinary excretion of 17-ketosteroids, without an increase in the excretion of glucocorticoids; in fact, a significant reduction in the excretion of glucocorticoids often occurs. The excretion of estrogens and pregnanediol chromogens, presumably synthesized by the overactive adrenal cortex, is also increased. The hormonal relationships in the untreated patient, based upon current understanding of the syndrome, are represented diagrammatically in Fig. 1. The anterior pituitary

gland secretes excessive amounts of adrenocorticotropic hormone, which stimulates the adrenal cortex to increased output, primarily of androgenic-type steroids. Bartter and associates[2] first reported that, although these patients responded to the administration of ACTH with a further increase in 17-ketosteroid output, they showed insignificant increases in the excretion of glucocorticoids. The glucocorticoids are active inhibitors of the anterior pituitary output of ACTH, while the androgenic steroids either do not possess this property or are relatively ineffective in such depression. For this reason, Bartter suggested that the primary defect in congenital adrenal hyperplasia is the inability of the adrenal cortex to synthesize readily the glucocorticoids, e.g., hydrocortisone. Consequently, the anterior pituitary secretes excessive amounts of ACTH which then overstimulates the adrenal cortex in an attempt to evoke a "normal" output of glucocorticoids. The adrenal cortex, responding in the only way that it can, produces an increased amount of androgenic steroids, resulting in the symptoms of virilism. The excessive secretion of androgens and estrogens suppresses the gonadotropic function of the anterior pituitary. This theory of defective glucocorticoid synthesis is currently accepted as the most plausible explanation of the etiology of the adrenogenital syndrome.

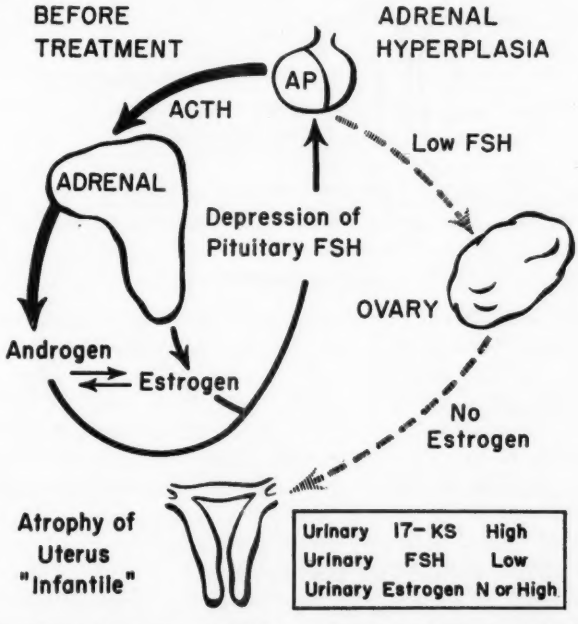


Fig. 1.—A diagrammatic representation of the probable interrelationships in the untreated patient with congenital adrenal hyperplasia. Before treatment pituitary corticotropin causes excessive secretion of androgen and estrogen from the adrenal cortex. The excessive androgen output counteracts any effect of estrogen on sex organs, and the increased secretion of androgen and estrogen inhibits the release of gonadotropin from the pituitary, thereby preventing normal ovarian function.

When cortisone or hydrocortisone is administered exogenously (Fig. 2), the body needs for glucocorticoids are supplied. As a result the anterior pituitary output of ACTH is inhibited and the overstimulation of the adrenal cortex ceases. Consequently, there occurs a sharp decrease in the adrenocortical synthesis of androgens, virilization is reversed, normal anterior pituitary-ovary

relationships are established, gonadotropic hormones are secreted in adequate amounts, estrogens are then produced by the ovary, and feminization results. As a part of the feminization process, normal breast and uterine development occurs and regular menses are established.

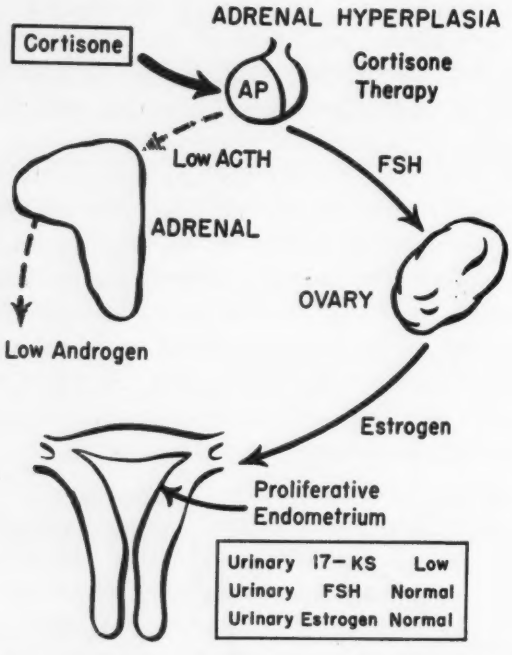


Fig. 2.—Cortisone therapy inhibits the excessive output of corticotropin, thereby decreasing adrenal secretion of androgen and permitting gonadotropic activity by the pituitary, ovarian secretion of estrogen, and normal actions of estrogens on secondary sex development.

Case Report

Miss N. N., a 16-year-old white girl, was first seen by us on Dec. 29, 1949, with a chief complaint of amenorrhea. The patient was brought in by her mother who stated that the child had "menstruated" only once on Oct. 19, 1948, at the age of 15 years; this period lasted for 3 or 4 days and required approximately 3 to 4 pads per day. There were no associated clots and no dysmenorrhea. The patient had never had any bleeding before or since. There was no history of vaginal discharge, abdominal pain, or cramps.

The past history, as determined from the mother, disclosed normal development. She started walking at the age of 17 months without ever crawling, and began to talk at the age of 10 to 12 months. There were no difficulties in school; she was normally alert and was a sophomore in high school at the time that she was first seen. The only significant past history was of pylorospasm at the age of 5 days which was treated medically for a period of 6 months. The systemic history was negative. Her fingernails were always soft, but never brittle; the hair was quite oily, but the skin was normal with the exception of moderate acne. She had no difficulty sleeping and gave no history of intolerance to cold or inclement weather. She was cared for by a reputable pediatrician during the first year of life and was also seen by two other pediatricians during the course of her pylorospasm. At no time was any abnormality described by them. The mother stated that the child's voice was always a bit deeper than that of other girls, but that it had never seemed masculine to her. Approximately three years prior to her first visit, rather pronounced growth of hair on the legs, arms, and abdomen began, but was felt by the mother to be a familial characteristic. Approximately three years prior to this initial examination, however, the mother noted by her own examination an increase in growth of the child's external genitals, but did not seek medical advice at

that time. Approximately six months prior to our consultation, the patient was seen by the family physician who referred her to a gynecologist in the area who referred her to our care. The only significant familial history was one of paternal diabetes, and a history of mild nephritis with edema of the feet and legs in the mother approximately 6 years prior to the patient's birth.

Physical examination showed a well-developed, muscular, but typically female-appearing, shy girl with a somewhat husky, almost masculine voice. Her height was 152 cm., weight, 50 kilograms, blood pressure, 110/76. The arms and thighs were unusually hairy, but there were only a few coarse hairs over the chest and around each nipple. The escutcheon was typically female in outline, with only a few coarse hairs extending from the mons to the umbilicus. There was a faint suggestion of fullness in the region of the right pole of the thyroid. The breasts were hypoplastic and undeveloped with practically no subcutaneous adipose tissue. The arms and legs were quite firm, muscular, and of masculine proportions. The acral parts were well formed and not disproportionate. Her gait was somewhat slovenly, but this seemed to be compatible with her age and personality. The remainder of the general physical examination was entirely normal.

Pelvic examination showed marked hypertrophy of the clitoris, measuring 4 cm. in length, by 2 cm. in diameter, and with no opening on either dorsal or ventral surface. The ventral surface was slightly triangular, however, without a definite raphe. Just below the base of the clitoris, a normal urethra was easily visualized. Immediately posterior to and almost opening into the urethra was another opening (the vagina) approximately 2 mm. in diameter which was sounded and found to measure 9.4 cm. in length. On rectoabdominal examination, a tiny uterus, 3.8 cm. long by 2.5 cm. wide, was palpated in the midline; it seemed to be normal in shape and mobility. Both ovaries were palpated and were normal in size. There was no intrarectal pathology.

The urine and complete blood count were normal. The basal metabolism rate was minus 8 per cent. Determinations of 17-ketosteroids were performed on four separate 24 hour specimens with a daily average excretion of 45.9 mg. Urinary estrogens were positive at 54 rat units and urinary gonadotropins were negative at 3 mouse units. The eosinophil count was 112 per cubic millimeter. The fasting blood sugar was 70 mg. per cent. Serum electrolytes were normal except that the chlorides were elevated, varying between 110 and 117 meq. per liter. Serum calcium and phosphorus were 4.53 and 1.71 meq. per liter, respectively.

After complete evaluation, the patient was admitted to the hospital where, on April 22, 1950, a laparotomy was performed. On exploration of the abdomen, the uterus, tubes, and ovaries were plainly identified. The uterus was small, symmetrical, and seemed to be typically infantile; it was wedge shaped in appearance and measured approximately 3 cm. transversely by approximately 1.3 cm. in the anteroposterior dimension. To palpation, the entire uterus measured approximately 3.8 cm. in length. Both tubes were normal in length and presented normal fimbriated ends bilaterally. The ovaries each measured 2 by 2½ cm. in diameter, were symmetrical, small, shiny, white and glistening, but without any evidence of tumor. Both ovaries were slightly more firm than the normal to palpation and were biopsied. On being cut, they presented multiple small cystic areas. An incidental appendectomy also was done. The hypertrophied clitoris then was excised and a perineotomy was performed. Microscopic examination of the tissue removed disclosed a multiplicity of primordial follicles with a few of the follicles enlarged and lined by granulosa cells. The clitoris was not abnormal and the appendix was normal. The wounds healed satisfactorily and the patient was discharged on the eighth postoperative day.

On June 8, 1952, a pretreatment control period of study was begun. During this time 17-ketosteroids, estrogens, gonadotropins, and pregnanediol excretions were determined weekly, and body temperature and vaginal cytology were determined daily. One month later the patient was started on oral cortisone,* 50 mg. daily for 60 days. Throughout the period of treatment, she was studied intensively with daily vaginal smears and basal body temperature readings; in addition, weekly determinations of urinary 17-ketosteroids, estrogens, gonadotro-

*Cortisone acetate (Cortone) was supplied by Dr. E. Alpert, Merck & Company, Inc.

pins and pregnanediol were performed. Biweekly determinations of blood electrolytes, sugar, and eosinophil count were also made. Clinical progress, including measurement of blood pressure, was checked every two weeks. The 17-ketosteroid excretion dropped consistently to well below 10 mg. per 24 hours, with an average urinary excretion of 8 mg. per 24 hours. After 30 days of this dosage, the 17-ketosteroid excretion rose to and remained at approximately 20 to 24 mg. per 24 hours. Cortisone dosage was then increased to 62.5 mg. daily with a subsequent mild reduction in the excretion of 17-ketosteroids, but still at levels of approximately 12 to 15 mg. per day. The cortisone dosage was then further increased on the ninetieth day to 75 mg. orally with no appreciable change in the level of 17-ketosteroid excretion. On the one hundred fifteenth day of therapy, the patient was started on 50 mg. of cortisone intramuscularly over a period of approximately one month, which brought about marked reduction in the urinary 17-ketosteroid excretion. The patient was then maintained on 75 mg. of cortisone orally daily, but the level of 17-ketosteroid excretion still exceeded 10 mg. a day. Hence, a further increase was made in oral cortisone dosage of 100 mg. per day on the one hundred eighty-second day of treatment. She was maintained on this dosage through the four hundredth day of treatment, which dosage kept the 17-ketosteroid output at an average of 10 mg. per 24 hours.

The patient was married on June 5, 1953. She remained in this area for approximately two months during which time the 17-ketosteroid remained approximately 10 mg. per 24 hours while the patient was on a dosage reduced by her to 75 mg. per day of cortisone. The patient, whose husband was in the Navy, left town and has not been seen by us since, although we have heard from her mother that she is continuing thyroid and cortisone and is menstruating normally and feeling quite well.

Methods

Urinary 17-ketosteroids were determined according to the method of Drekter and co-workers,[6] total urinary estrogens by a modified Allen-Doisy procedure using adult spayed female rats, free pregnanediol by a slight modification of the method of Sommerville and others,[7] and gonadotropins by the method of Bradbury[8] using immature female mice. Urine sodium and potassium were determined by flame photometry, and urine chloride was determined by the method of Schales and Schales,[9] urine calcium by the method of McCrudden,[10] and urine phosphorus by the method of Subbarow.[11] Circulating eosinophils were measured by the method of Hills and associates,[12] and blood glucose by a modification of Folin's method using Somogyi's[13] method of protein precipitation with zinc hydroxide. Serum calcium was determined by the method of Kramer and Tisdall,[14] and serum sodium, potassium, chloride, and phosphorus were measured by the methods previously listed.

Results

The data accumulated in a year of intensive study are too extensive for presentation in tabular form. However, results for 17-ketosteroid and estrogen excretion in relation to cortisone dosage, basal body temperature, and menstrual pattern during a year of continuous study are presented in Table I and in Figs. 3, 4, and 5.

The output of 17-ketosteroids ranged between 40 and 50 mg. daily during control periods prior to the study, except for an increase to 65 mg. during an upper respiratory infection. Oral cortisone in amounts of 50 mg. daily brought about a prompt decrease in 17-ketosteroid excretion to 7.5 mg. on the fourth day. Wilkins recommends that for optimum effect the dosage be adjusted to keep the excretion below 8 mg. daily. The 17-ketosteroid excretion remained below 8 mg. for about 23 days, then rose to levels of 20 to 30 mg., which were

maintained for over 3 months in spite of steplike increases in cortisone dosage. Only by the intramuscular administration of 50 mg. cortisone daily for 1 week could the excretion of 17-ketosteroids be decreased to below 8 mg. daily. The oral administration of 100 mg. daily of cortisone was required to maintain the level of 17-ketosteroid excretion at 8 to 10 mg. daily. Oral cortisone dosage and 17-ketosteroid excretion were maintained at these levels for approximately 6 months.

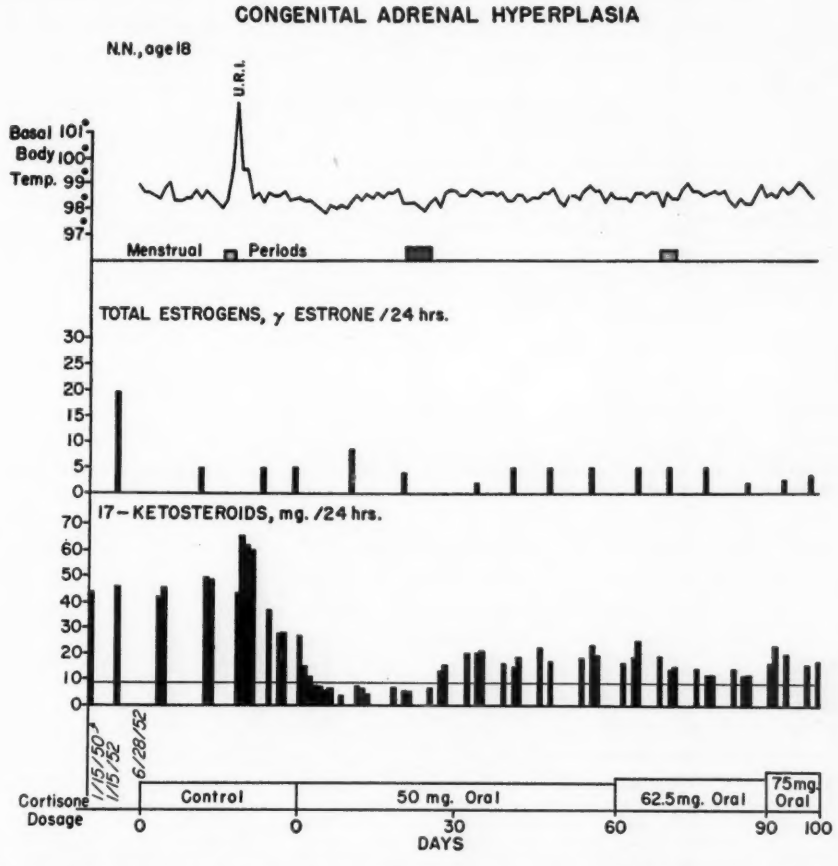


Fig. 3.—Effects of oral cortisone in suppressing the 17-ketosteroid excretion in a female pseudohermaphrodite. Initially 50 mg. daily produced prompt suppression, but an "escape" from the inhibitory effect of cortisone occurred and 75 mg. daily was insufficient to suppress the 17-ketosteroid output below 8 mg. per day.

On one occasion during the control period, the excretion of estrogen was high, in agreement with the findings of other investigators that, in patients with this disorder, the adrenal cortex secretes increased amounts of estrogen.[1] Other values obtained immediately prior to cortisone therapy were in the normal range. After cortisone treatment was instituted, the estrogen excretion rose to 10 gamma per day, then decreased at the time of the first menstrual period. During the long interval that the 17-ketosteroid excretion was elevated to 20 to 30 mg., estrogen excretion remained consistently low with no cyclic variations. Once the 17-ketosteroid excretion was depressed to approximately 8 mg. daily, the estrogen excretion promptly increased to 15 gamma daily and showed cyclic increases and decreases corresponding to the regular menstruation periods. A marked increase in estrogen excretion occurred during the 6 weeks prior to marriage, simultaneously with a prolonged period of amenorrhea, even

though the 17-ketosteroid excretion showed no change. To explain these findings one is forced to speculate regarding the influence of emotional stresses incident to marriage upon endocrine balance.

TABLE I. 17-KETOSTEROID EXCRETION IN RELATION TO CORTISONE DOSAGE

DATE	CORTISONE DOSAGE (MG./DAY)	NUMBER OF DAYS	NUMBER OF URINE SPECIMENS	17-KETOSTEROIDS (MG./24 HOURS*)	
				RANGE	MEAN
1/13-15/1950	0	3	3	41.5-46.9	44.0
2/15-16/1952	0	2	2	40.9-51.4	46.2
6/29-7/28/52	0	30	11	27.4-65.1	46.0
7/29/52	50 (oral)	1	1		26.8
7/30/52	50 (oral)	1	1		15.2
7/31/52	50 (oral)	1	1		11.3
8/1/52	50 (oral)	1	1		7.5
8/2-8/24/52	50 (oral)	23	11	3.8- 7.4	6.0
8/25-9/27/52	50 (oral)	34	13	13.0-23.4	18.5
9/28-10/25/52	62.5 (oral)	28	12	11.6-25.2	15.5
10/26-11/21/52	75 (oral)	27	12	10.6-23.6	16.8
11/22-12/23/52	50 (I.M. 3 times a day)	32	15	19.9-31.1	27.2
12/24-1/2/53	50 (I.M. daily)	10	5	4.9-27.7	
1/3-1/24/53	75 (oral)	26	9	6.0-12.0	9.0
1/25-6/4/53	100 (oral)	130	52	4.8-12.4	9.5
6/5-7/28/53	100 (oral)	54	9	6.1-12.7	10.3
9/3-4/53	75 (oral)	2	2	8.3-10.3	9.3

*Occasional low 17-ketosteroid values on incomplete urine collections were corrected on the basis of mean creatinine excretion.

TABLE II. URINARY 17-HYDROXYCORTICOIDS AND PREGNANEDIOL CHROMOGENS

DATE	CORTISONE DOSAGE (MG./DAY)	17-KETOSTEROIDS (MG./24 HOURS)	17-OH CORTICOIDS (MG./24 HOURS)	PREGNANEDIOL* (MG./24 HOURS)	PREGNANETRIOL† (MG./24 HOURS)
7/1/52	0	41.7	0	12.7†	58.2
7/25/52	0	36.6	0	4.9	
8/10/52	50 (oral)	6.8	6.3	0.5	
8/19/52	50 (oral)	5.2		2.4†	1.8
8/23/52	50 (oral)	6.9	7.4		
8/30/52	50 (oral)	20.0		18.4	
9/6/52	50 (oral)	16.3	5.2	0	
9/13/52	50 (oral)	22.1		11.5	
1/6/53	75 (oral)	11.9		1.2	
1/13/53	75 (oral)	9.7		1.8	
1/19/53	75 (oral)	6.0	11.3	0	
1/25-6/4/53	100 (oral)	4.8-12.4		0	

*According to the method of Sommerville and others.[7]
†According to the method of Bongiovanni.[17]

The excretion of pituitary gonadotropins showed little correlation with the establishment of cyclic menstrual periods, or with changes in 17-ketosteroid or estrogen excretion. The method used for assay of gonadotropins measures primarily follicle-stimulating hormone, FSH, but does not exclude the possible influence of luteinizing hormone. In general the gonadotropin excretion was low, with frequent values of less than 6 M.U. daily.

The excretion of pregnanediol chromogens was elevated prior to treatment (Table II) in agreement with reports in the literature that patients with adrenal hyperplasia excrete large amounts of pregnanediol and other pregnane derivatives.[15] Urinary "pregnanediol" was considerably decreased during the period of low 17-ketosteroid excretion (specimens of August 10 and 19), but increased

again when the 17-ketosteroid excretion rose to approximately 20 mg. daily (specimens of August 30 and September 13). No detectable quantities of "pregnanediol" were present in later samples when the 17-ketosteroid excretion was maintained below 10 mg. daily. The two values of 1.2 and 1.8 mg. obtained 10 and 3 days prior to the menstrual period which followed the administration of intramuscular cortisone (specimens of January 6 and 13) might have been due to progesterone from corpus luteum activity. The basal body temperature was not conclusive of ovulation in this cycle, however. Unfortunately, pregnanediol determinations were not obtained during the two cycles immediately after marriage when the temperature curve suggested an ovulatory pattern.

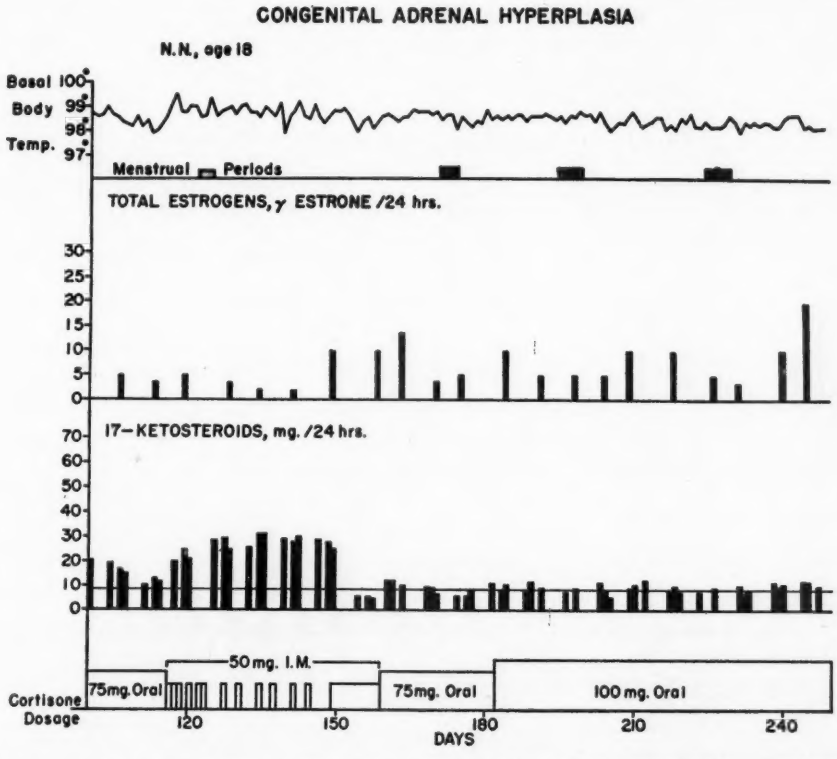


Fig. 4.—Effects of cortisone treatment in congenital adrenal hyperplasia, continued. The 17-ketosteroid output was suppressed below 8 mg. per day by 50 mg. intramuscular cortisone, and maintained at approximately this level with 100 mg. oral cortisone daily. Cyclic changes in estrogen excretion coincided with menstrual periods.

Studies by Bongiovanni[16] and others have indicated that the presence of the abnormal metabolite, pregnanetriol, in the urine of patients with suspected congenital adrenal hyperplasia is diagnostic of this syndrome. Adequate cortisone treatment results in the disappearance of pregnanetriol from the urine. In preliminary studies with Bongiovanni's[17] method of chromatographic separation on urine specimens stored in the freezer for 3 years, we have found 58.2 mg. pregnanetriol in the urine prior to treatment, and 1.8 mg. in a specimen during cortisone treatment when the 17-ketosteroid excretion was less than 8 mg. daily. Undoubtedly this pregnanetriol accounts in part for the high values for "pregnanediol chromogens" in the urine before treatment and during periods of inadequate cortisone dosage.

Repeated determinations of urinary 17-hydroxycorticoids by the method of Reddy and his co-workers[18] indicated the absence of detectable quantities

in the urine prior to treatment (Table II). The daily excretion increased to 5 to 7 mg. with a cortisone dosage of 50 mg. and to 11 mg. when the cortisone dosage was increased to 75 mg. daily.

In Table III are presented mean values for serum and urine electrolytes for the various periods of cortisone administration for patient N. N. No significant changes in serum electrolytes were observed, although a tendency to an increase in serum sodium and a decrease in serum potassium with the higher dose of cortisone is apparent. Daily variation in urinary sodium, potassium, and chloride values was marked due to the fact that the intake of these electrolytes was not controlled. Cortisone administration did not significantly alter the level of excretion.

TABLE III. SERUM AND URINARY ELECTROLYTES DURING CORTISONE TREATMENT

PERIOD	CORTISONE DOSAGE (MG./DAY)	NUMBER OF DAYS	NUMBER OF SPECIMENS	URINE (MEQ./DAY) Na	K	Cl	Ca	P
Control	0	30	9	129.7	44.2	110.7	6.58	41.7
7/29-8/24/52	50 (oral)	27	9	138.1	58.0	150.3	6.2	38.9
8/25-9/27/52	50 (oral)	34	12	118.3	33.4	134.3	8.3	43.2
9/28-10/25/52	62.5 (oral)	28	8	111.7		123.6	9.2	34.6
10/26-11/21/52	75 (oral)	27	6	140.7	42.5	127.0	7.52	42.9
11/22-12/23/52	50 (I.M. 3 times a day)	32	6	140.8	38.9	136.7		
12/24/52-1/2/53	50 (I.M. daily)	10	5	139.1	41.9	139.4	3.6*	38.3
1/3-1/24/53	75 (oral)	26	9	178.0	44.0	177.0	6.1	39.2
1/25-6/4/53	100 (oral)	130	50	137.4	40.2	142.0	7.44	42.5

PERIOD	CORTISONE DOSAGE (MG./DAY)	NUMBER OF DAYS	NUMBER OF SPECIMENS	SERUM (MEQ./L.) Na	K	Cl	Ca	P
Control	0	30	2	142.0	5.89	113.0	5.85	1.97
7/29-8/24/52	50 (oral)	27	1	141.0		111.0	5.75	2.64
8/25-9/27/52	50 (oral)	34	1	147.0	6.04	116.0	5.75	
9/28-10/25/52	62.5 (oral)	28	2	146.5	5.50	106.0	5.48	2.63
10/26-11/21/52	75 (oral)	27	1	142.5	4.20	108.0	5.2	2.5
11/22-12/23/52	50 (I.M. 3 times a day)	32	2	149.0	4.52	109.0	4.55	2.67
12/24/52-1/2/53	50 (I.M. daily)	10	1	149.0	4.80	104.0	4.95	2.67
1/3-1/24/53	75 (oral)	26	1	152.0	4.71	112.0	4.5	2.73
1/25-6/4/53	100 (oral)	130	8	148 0	4.29	107.0	5.68	2.42

*Only 3 specimens analyzed.

Changes in body weight and blood pressure during the long period of cortisone treatment were not significant. The patient gained approximately 6.8 kilograms in 3 months after her marriage, but this gain could be accounted for by an increase in calorie intake. Systolic blood pressure ranged between 108 and 128, with diastolic pressure between 70 and 86; there was no evidence of any progressive increase during treatment. As expected from the known eosinopenic action of cortisone, the eosinophil count decreased from control levels of 103 to 214 to levels of 50 to 100 cells per cubic millimeter.

Sugar appeared in the urine during the sixth month of treatment when the dosage was 75 mg. daily; and was persistent thereafter, although usually only in trace amounts. No increase in blood sugar from fasting levels of 50 to 80 mg. per 10 ml. was observed, and a normal glucose tolerance test was obtained in the tenth month of treatment. During the tolerance test, glucose appeared in the urine only in the one-hour specimen, when the blood sugar was 157 mg. per 100 ml., indicating a normal renal threshold for glucose. Proteinuria in trace amounts was found intermittently during the ninth to twelfth months of treatment.

Vaginal smears were taken daily during the first 10 months of the study. Cytological evaluation showed a markedly hypotrophic state of the vaginal epithelium with many basal cells and an exceedingly low percentage of cornified cells prior to cortisone administration. Although the dosage was inadequate to maintain suppression of the androgen secretion during the early period of cortisone treatment, nevertheless the percentage of basal cells decreased markedly, with a corresponding increase in precornified cells and a slight increase in cornified cells. With adequate cortisone dosage, basal cells all but disappeared, and the percentage of cornified cells reached normal levels with cyclic variations corresponding fairly well with menstrual periods and with changes in urinary estrogen excretion.

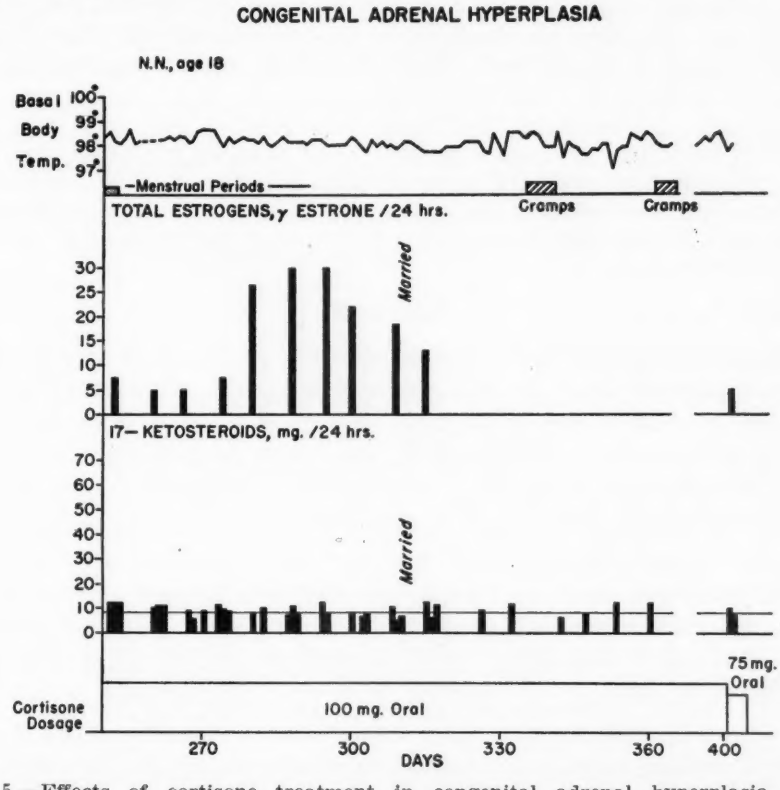


Fig. 5.—Effects of cortisone treatment in congenital adrenal hyperplasia, continued. Marriage and the accompanying emotional stresses caused changes in the estrogen excretion and in the menstrual pattern, without altering cortisone dosage or 17-ketosteroid output.

Clinical Results

Encouraging clinical progress, with feminization, occurred even though the androgen secretion was not suppressed sufficiently to keep the 17-ketosteroid excretion below the 8 mg. limit recommended by Wilkins. One of the most striking changes was the improvement in the patient's attitude which was so marked at first as to border on euphoria. Her self-confidence improved, she became interested in and attractive to boys, and was married 10 months after starting cortisone treatment.

The breasts increased significantly in size, particularly during the last 6 months of the study when the androgen output was kept at about 9 to 10 mg. daily. Hair growth on the extremities became much softer and lighter, and facial hair disappeared except for light fuzz. Acne cleared and considerable feminization of the figure occurred. Several examiners noted an increase in the pitch of the voice.

Menstrual bleeding in the form of bright-red blood for 4 days started on the twenty-second day of cortisone therapy when the 17-ketosteroids were depressed to levels of 5 to 6 mg. During the 4 months that the 17-ketosteroids excretion was elevated to levels of 15 to 30 mg., only 2 episodes of one or two days of brown discharge occurred. A normal period occurred 23 days after the start of the daily intramuscular cortisone, which depressed the 17-ketosteroid output below 8 mg. per day. Two normal periods of bleeding followed at intervals of 28 and 30 days, during the time when the cortisone dosage was 100 mg. daily and the 17-ketosteroid output was approximately 10 mg. per day. Another period of slight brown discharge occurred 32 days later, then no bleeding at all for 65 days. Twenty-five days after the patient's marriage, with no change in cortisone dosage or in level of 17-ketosteroid output, she had a normal 5 to 6 day period with the heaviest blood loss ever experienced, followed 25 days later by another normal 4 day period. With the two periods after marriage, for the first time, the patient had dysmenorrhea.

In general, the curve of basal body temperature was erratic and showed no sustained pattern. A pattern suggestive of possible ovulation occurred only 4 times: immediately after the start of cortisone treatment when the 17-ketosteroid excretion was below 8 mg., when the 17-ketosteroids were depressed below 8 mg. with intramuscular cortisone, and during the two cycles that followed the patient's marriage.

Comment

It appears that no definite dosage schedule of cortisone can be prescribed for the inhibition of pituitary corticotropin in patients with congenital adrenal hyperplasia, nor can a specific formula be set up for decreasing the output of urinary 17-ketosteroids. Variations in the dosage of cortisone, or even in the route of administration of the drug are required to bring about clinical responses as well as the objective result of a decrease in the urinary excretion of 17-ketosteroids. Our patient required 100 mg. oral cortisone to decrease the 17-ketosteroid excretion to 10 to 12 mg. per day, which level of adrenal cortical inhibition apparently was not quite sufficient to permit full ovulatory ovarian function, although it was adequate to permit estrogen secretion and feminization.

We were reluctant to give more than 100 mg. cortisone daily for fear of producing overdosage symptoms typical of Cushing's syndrome. Although the patient showed no clear-cut symptoms of toxicity, the tendency toward an increase in serum sodium and decrease in serum potassium, together with persistent glycosuria and occasional proteinuria indicated that the dose of 100 mg. per day was near the maximum she could tolerate. The persistent glycosuria may indicate an unusual sensitivity of this patient to the anti-insulin effect of cortisone, possibly related in some way to the family history of diabetes mellitus.

Intramuscular cortisone, 50 mg. daily, produced in patient N. N. somewhat greater depression of the adrenal cortex than 100 mg. orally, corroborating the findings of Wilkins[5] that cortisone given intramuscularly is at least twice as effective as orally.

The apparent "escape" from the initial effectiveness of cortisone in this patient is difficult to explain. Although the 17-ketosteroid excretion originally showed a prompt decrease on the daily dosage of 50 mg. cortisone, the level of

excretion gradually increased and continued to increase even with steplike increases in cortisone dosage. After this "escape," cortisone in twice the original amount, 100 mg. per day, did not produce as effective control of the adrenal hyperfunction as did 50 mg. originally.

Summary

The results of continuous treatment of a 16-year-old girl with congenital adrenal hyperplasia with cortisone for a period of one year have been evaluated. Cortisone in amounts of 100 mg. orally or 50 mg. intramuscularly daily was required to suppress adequately the adrenal androgen secretion. At this dosage level considerable feminization occurred with normal breast development, cornification of the vaginal smear, regular menstruation, and a decrease in hirsutism. Although the urinary estrogen excretion and vaginal smear cornification showed cyclic changes coinciding with the menstrual periods, no positive evidence of ovulation was obtained during the period of study.

References

1. Wilkins, L., Lewis, R. A., Klein, R., Gardner, L. I., Crigler, J. F., Jr., Rosemberg, E., and Migeon, C. J.: J. Clin. Endocrinol. **11**: 1, 1951.
2. Bartter, F. C., Albright, F., Forbes, A. P., Leaf, A., Dempsey, E., and Carroll, E.: J. Clin. Invest. **30**: 237, 1951.
3. Jailer, J. W., Louchart, J., and Cahill, G. F.: J. A. M. A. **150**: 575, 1952; J. Clin. Invest. **31**: 880, 1952.
4. Kelley, V. C., Ely, R. S., and Raile, R. B.: J. Clin. Endocrinol. **12**: 1140, 1952.
5. Wilkins, L., Gardner, L. I., Crigler, J. F., Jr., Silverman, S. H., and Migeon, C. J.: J. Clin. Endocrinol. **12**: 257, 1952; **12**: 277, 1952.
6. Drekter, I. J., Pearson, S., Bartczak, E., and McGavack, T. H.: J. Clin. Endocrinol. **7**: 795, 1947.
7. Sommerville, I. F., Gough, N., and Marrian, G. F.: J. Clin. Endocrinol. **5**: 247, 1948; Smith, O. W.: J. Clin. Endocrinol. **10**: 496, 1950.
8. Bradbury, J. T., Brown, E. S., and Brown, W. E.: Proc. Soc. Exper. Biol. & Med. **71**: 228, 1949.
9. Schales, O., and Schales, S. S.: J. Biol. Chem. **140**: 879, 1941.
10. McCrudden, F. H.: J. Biol. Chem. **66**: 187, 1911.
11. Fiske, C. H., and Subbarow, Y.: J. Biol. Chem. **66**: 375, 1925.
12. Hills, A. G., Forsham, P. H., and Finch, C. A.: Blood **3**: 755, 1948.
13. Folin, O.: J. Biol. Chem. **67**: 357, 1926; Somogyi, M.: J. Biol. Chem. **86**: 655, 1930.
14. Kramer, B., and Tisdall, F. F.: J. Biol. Chem. **47**: 475, 1921.
15. Butler, G. C., and Marrian, G. F.: J. Biol. Chem. **119**: 565, 1937.
16. Bongiovanni, A. M., Eberlein, W. R., and Cara, J.: J. Clin. Endocrinol. **4**: 409, 1954.
17. Bongiovanni, A. M., and Clayton, G. W., Jr.: Bull. Johns Hopkins Hosp. **94**: 180, 1954.
18. Reddy, W. J., Jenkins, D., and Thorn, G. W.: Metabolism **1**: 511, 1952.

THE TREATMENT OF PREMENSTRUAL TENSION WITH A COMBINATION OF AN ANTIHISTAMINIC AND A THEOPHYLLINE DERIVATIVE

THOMAS H. MCGAVACK, M.D., HERBERT J. SPOOR, M.D., MARTIN L. STONE, M.D., AND SIDNEY PEARSON, PH.D., NEW YORK, N. Y.

(From the New York Medical College, Metropolitan Medical Center Research Unit and the Department of Gynecology, New York Medical College)

AMONG primitive peoples, variations in emotional status and mental and physical efficiency during the menstrual cycle, commonly ascribed to the cycles of the moon and the tides, were often made the basis for ritualistic observances. Today we know that these ideas have no foundation in fact. Ellis[1] and more recently Hoskins[2] have summarized in masterly fashion the literature relating to the psychological fluctuations attendant upon the various phases of the menstrual cycle. Smith[3] has summarized the premenstrual findings. These include a reduction of progesterone with intensification of the oxidation of estrogen, a return of urinary follicle-stimulating hormone, and an increase in luteotrophin and antidiuretic substance, indicating stimulation of the hypophysis before and at the beginning of menstruation.

These alterations in hormonal balance are attended by certain readily recognized symptoms and signs. These may be so mild as to go virtually unnoticed by the majority of women, but in some individuals they are sufficiently severe to interfere materially with the performance of the usual daily tasks. To this state Frank[4] was the first to give the name "premenstrual tension." Any aggravation of one or more of the symptoms or signs which may precede the onset of menstrual flow may constitute a symptom of this condition. Headache, depression, irritability, "inward tension," sensitive breasts, and pelvic distress are the usual complaints. Abdominal bloating or fullness, lower abdominal cramps, backache, and legache are less frequently noted. In some instances, acne may be exaggerated, or cutaneous, subcutaneous, and mucosal hemorrhages and obvious edema may also be present. While there are a number of theories as to the causes of premenstrual tension, the retention of water and electrolytes seems to be a frequent, if not an invariable, concomitant.[5, 6] The regularity of the flow is not ordinarily disturbed, but the amount may be normal or profuse with "staining" one to two days before full establishment.[3] The condition has always been difficult to control hormonally and there is great divergence of opinion regarding its proper endocrine treatment.[3, 6-17] There is general agreement that the major factor causing resistance to endocrine therapy is directly associated with the degree of water and electrolyte retention. It is further believed that an allergy, perhaps to endogenous products, i.e., hormones, or debris associated with molimina, often complicates the picture.[3]

Evidence is increasing to indicate that premenstrual edema is best treated by therapy immediately directed to the removal of water and salt.[5, 7, 9, 10, 18] Ammonium chloride has met with some success, but is not always well tolerated, and tends to alter acid-base balance. Simple restriction of salt has not been very successful either, because this is usually distasteful to the young active woman whose school or business activities, household duties, and children leave little time for special dietary care of herself. Several workers, therefore, have investigated the merits of the theophylline series of compounds for possible application to this particular type of water and salt retention.[5, 7, 17-24]

In view of the proved usefulness of certain members of this group of compounds and the distressing nature of the water and salt retention in premenstrual tension, it was decided to group patients according to the degree of water and salt retention, the better to observe the mechanism of action of this type of diuretic.

Methods and Procedure

Medicinal Preparation.—Because of the already considerable laboratory[18, 19, 25, 26] and clinical evidence[5, 8, 18, 23] of its ability to further the excretion of salt and water, it was decided to use for these studies a tablet consisting of 2-amino-2-methyl-1-propanol-8-bromotheophyllinate, 50 mg., and pyrilamine maleate, 30 mg.* Although Grote[19] had previously reported that the 8-bromotheophyllinate moiety was alone responsible for the diuretic action of this preparation, Bickers found clinically that neither 8-bromotheophyllinate nor pyrilamine maleate alone was therapeutically active. Consequently, the mixture was employed in this study.

Preliminary Study.—Although this material (neoBromth) had been previously used therapeutically in human beings, before starting the present water study, we carried out human toxicological studies in 9 subjects[27] to establish dose limits. No side effects from dosages up to 4 tablets (320 mg.) four times daily (a total daily dose of 1,280 mg.) for periods of 4 consecutive weeks of administration were found. No changes were observed in the urinary formed elements nor in the excretion of albumin. The blood counts were not adversely influenced by the drug and several measures designed to test the function of the liver showed no alterations in this organ.

Inasmuch as the preparation to be employed had been shown both in small laboratory animals and in man to produce diuresis,[19, 20, 25, 26] and, as it is well known that theophylline itself increases renal blood flow and glomerular filtration without damage to the parenchymal cells, it seemed of interest to determine whether or not there was any action on the renal tubule, and whether such action was antagonistic to that of vasopressin. In two water-loading experiments, there was very little inhibition, if any, of the vasopressin effect, a result similar to that observed by Miller.[26] We were struck, however, with the diuretic action of the material, and our ability to maintain this for a considerable period of time by continuous administration. Nine subjects were maintained on constant intakes of food and salt and were allowed water ad libitum during a "fore" period of one week, a test period with the drug preparation for 10 days, and a one week "recovery" period. Fluid intake and urinary excretion for volume, sodium potassium, and chloride were measured throughout all periods of observation. Striking diuresis occurred in each instance with a tendency for a wearing-off effect to be observed by the fourth or fifth day, a change which was usually reversible by a substantial increase in dosage. This diuresis involved

*This material was furnished to us through the courtesy of Dr. J. M. Holbert of the Brayten Pharmaceutical Company under the trade name, neoBromth.

TABLE I. CONCENTRATION OF URINARY SODIUM UNDER THE INFLUENCE OF neoBROMTH

PATIENT NO.	VOLUME (C.C.) OF URINE PER MEQ. OF SODIUM EXCRETED		RATIO OF EXCRETION OF CONTROL AND TEST PERIODS
	CONTROL PERIOD	TEST PERIOD	
1	59.7	13.0	4.5
2	23.0	8.2	2.8
3	19.9	2.4	8.2
4	14.3	1.9	7.5
5	12.1	7.8	1.6
6	11.5	8.4	1.4
7	17.9	6.6	2.7
8	67.7	40.9	1.7
9	25.9	4.0	6.5

TABLE II. TREATMENT OF PREMENSTRUAL TENSION WITH A COMBINATION OF AN ANTIHISTAMINE AND A THEOPHYLLINATE (neoBROMTH)*

TYPE OF PREMENSTRUAL TENSION	NO. CASES	NO. OF CONTROL CYCLES			NO. OF PLACEBO CYCLES			NO. OF CYCLES WITH neoBROMTH		RESULTS† (DEGREE OF IMPROVEMENT‡)				
		NO. CASES	AVER. PER CASE	RANGE	NO. CASES	AVER. PER CASE	RANGE	AVER. PER CASE	RANGE	NONE	SLIGHT	MODERATE	MARKED	COMPLETE
a. With edema	17	17	6.9	1-48	9	1.2	1-3	3.0	1-14	3 (7)	2 (2)	2	6	4
b. With water retention, but no obvious edema	12	11	2.0	1-12	9	1.4	1-3	2.3	1-5	1 (8)	2 (1)	3	6	0
c. Without recognizable water retention	14	13	2.0	1-8	8	1.0	1-1	1.9	1-5	4 (6)	4 (1)	4 (1)	2	0
Total	43	41			26					8	8	9	14	4

*Each tablet of this material contained 50 mg. of 2-amino-2-methyl-1-propanol-8-bromotheophyllinate and 30 mg. of pyrilamine maleate.
†Placebo cycles are shown in parentheses.
‡See text under "Methods and Procedure" for key to improvement.

an increased excretion of water, sodium, and chloride. This did not seem to be due simply to an increased glomerular filtration, as the concentration of sodium and chloride was invariably increased. In Table I may be found a summary of the concentration of sodium on the third day of administration as compared with the control period. In this table there are recorded the number of cubic centimeters of urine containing 1 meq. of sodium in the control period as compared with the third day of administration of neoBromth, 2 tablets (160 mg.) four times daily. It will be noted that, in every subject, administration of the compound was associated with an increased concentration of sodium, and that the ratio of the control to the test period concentration varied from 1.4 to 8.2 with an average ratio of 4.1. Subjects 1, 7, and 8 were in mild congestive failure at the beginning of the test run; the others had no signs of edema from any cause. All showed a urinary response to the action of the drug which cannot be accounted for on the basis of a simple anti-vasopressin effect.

In view of the absence of toxicity in effective doses, and the positive action upon the excretion of water and electrolyte, a series of patients with premenstrual tension was studied clinically while receiving neoBromth.

Selection and Classification of Patients.—Forty-three patients derived from the outpatient clinic and private practice, who presented the picture of premenstrual tension, were divided into three groups: (1) those with frank edema, of whom there were 17; (2) those with water retention as shown by marked changes in weight, tightness of shoes, rings, etc., but with no obvious edema, of whom there were 12; and (3) those without clinically recognizable water retention, of whom there were 14. They ranged in age from 14 to 50 years, with an average age of 26.9 years. There were 13, 16, 8, and 6 subjects in the second, third, fourth, and fifth decades of life, respectively.

Routine of Living and Control Cycles.—No special instruction in regard to the general habits of living was given, save that in the few days prior to the onset of periods, late and irregular hours and alcohol were to be avoided in so far as possible. During "control" cycles (Table II) various other therapeutic measures may have been tried, but during one or more cycles immediately prior to the use of neoBromth, the patient was observed while using no medication. In those who had been previously treated for considerable periods of time, several such cycles without medication had been experienced, so that no psychological factor was believed to be involved with the use of the present treatment. In addition to the "control" cycles, "placebo" cycles were employed in 26 subjects, where the question of reliability arose (Table II). These cycles were usually sandwiched between those for which the neoBromth was used. An identical-appearing tablet containing no medication was used in the same number and with the same frequency as the medication had been in the previous cycle or cycles. Where any beneficial effect was observed from the placebo the overall appraisal of action was modified accordingly. In no instance was any effort made to restrict salt or water intake, or to alter the amount of protein ingested.

The degree of improvement (Table II) was recorded as "none" if there was no change at all in the symptomatology as a result of administration of the drug; "slight" if some one presenting symptom was definitely improved or if the patient believed a general increase in the sense of well-being had been effected without striking relief in any specific symptom; "moderate" if some one symptom was completely relieved, or several manifestations showed definite change for the better without major improvement in any; "marked" if two or more presenting symptoms were completely relieved or major improvement was present in all of the manifestations; and "complete" if all of the manifestations of tension were fully controlled.

Dosage.—The frequency and amount of dose of neoBromth were varied to suit the individual needs. In general, the drug was started each cycle when the patient was aware of the first symptoms or could with certainty expect them. The individual dose varied from 1 to 2 tablets given two, three, or four times daily. In 3 instances, the medication was used continuously, but only half the premenstrually employed dose was used at other times. Of the remaining patients, one received medication for 10 days premenstrually, and 8 for 7, 21 for 5, 5 for from 3 to 6, and 5 for 3 days, respectively. In 3 instances, administration was continued for one or more days of menstrual flow because of the persistence of edema. From the trials made it appears that 2 tablets twice daily were about as effective as larger doses at the same or a greater frequency. Since actual water and salt losses were not measured, however, this is only an impression, and in individual cases of a resistant nature we believe it will pay to try more than a single level of dosage.

TABLE III. SYMPTOMATIC ANALYSIS OF THE THERAPEUTIC ACTION OF AN ANTIHISTAMINE-THEOPHYLLINE PREPARATION (NEOBROMTH)

MANIFESTATION	NO. CASES	DEGREE OF IMPROVEMENT OR NORMALIZATION					
		NONE	SLIGHT	MODERATE	MARKED	COMPLETE	
Menstrual Cycle:							
Less than 26 days	3	3	0	0	0	0	
More than 32 days	8	1	0	2	4	1	
Amount of flow:							
Moderate	12	0	0	0	0	0	Normal flow. Not altered by medication
Scanty	23	10	5	3	4	1	
Profuse	8	5	2	1	0	0	
Water retention	29	4	4	5	12	4	
Extreme nervous and mental symptoms	21	2	2	6	9	2	
Acne	22	6	1	5	6	4	
Headache	22	4	1	4	5	8	
Breast engorgement	17	2	1	4	2	8	
Gastrointestinal:							
Nausea	6	1	0	0	3	2	
Vomiting	5	1	0	0	3	1	
Constipation	6	0	0	1	1	4	
Right upper quadrant distress	1	0	0	0	0	1	
Pelvic:							
Fullness and/or "dragging down"	15	4	0	2	6	3	
Abdominal pain	15	0	1	4	7	3	
Back and/or leg pain	8	0	2	4	2	0	

Results

The results of these studies are summarized in Tables II and III. Of the 43 patients with premenstrual tension who received neoBromth, 8 were not benefited in any way, and slight, moderate, marked, and complete relief were obtained by 8, 9, 14, and 4 subjects, respectively. If we make a single group of the patients who obtained no or slight improvement and treat them as "unimproved," and consider the remainder of the patients to have obtained definite relief, then 16, or 37.1 per cent, were not relieved and 27, or 62.9 per cent, showed

improvement. This contrasts with the fact that only 5 of 26 patients who were given the placebo obtained any relief at all, and this was in the instances classified as "slight" to "moderate."

If we analyze the data for the three groups (Table II) in this same manner, then we see that in the patients of Group I with edema, 5 of 17, or 29.5 per cent, were not relieved and the remaining 12, or 70.5 per cent, were. In Group II, with water retention but no outspoken edema, 3 of 12 patients were not benefited, while the remaining 9, or 75 per cent, were. In the last group (III) without clinically recognizable water retention, 6 of 14 subjects, or 43 per cent, obtained satisfactory amelioration of symptoms. It is clear that the patients with recognizable water retention responded in better fashion than those without.

The major manifestations present in the 43 patients studied are recorded in Table III. Only 11 patients showed an intermenstrual interval above or below the normally accepted range of 26 to 32 days. In conjunction with the use of neoBromth there was a tendency to shorten the prolonged intervals toward normal. In 23 of the 43 patients, the menstrual flow was scanty; in 8 of these there was some increase in the amount of flow while taking neoBromth. There were 8 patients who had a profuse flow; this was definitely decreased in only one case while this medication was used.

Of all the manifestations, water retention was probably the one most consistently favorably influenced (Table III), and the nervous and mental symptoms of tension next. Breast engorgement, gastrointestinal symptoms, and pelvic manifestations were controlled in most patients, while marked improvement in headaches was observed in slightly over half of the subjects (Table III). Adolescent or pubertal acne with normal premenstrual periods of aggravation was improved in 15 of 22 cases, or 68 per cent, by the use of neoBromth.

Comment

For the most part the cases of premenstrual tension selected for this study were difficult ones which had not improved by the use of various regimens of hormonal and sedative therapy. This was particularly true of the subjects with obvious edema. Seven of these had been under observation by one of us (T. H. M.) for a year or more with little or no relief of edema in association with various combinations of hormone therapy.

The mechanism of premenstrual tension, and particularly the water retention, seems still in doubt. Some of the factors concerned have been mentioned in introducing this study. It seems to be generally agreed that there is some imbalance between estrogen and progesterone production and activity, but the relative role played by each and the influence of alterations in other hormones such as the antidiuretic principle of the posterior pituitary is not clear. The favorable influence of neoBromth does not seem to be that of a simple vasopressin antagonist or a mineralo- or glucocorticoid protagonist, for *both* the urinary volume and concentration of sodium are increased. This action more nearly mirrors or opposes that of both androgen and estrogen and it may be that this is precisely the crux of its beneficial influence. Not only the present study but also that of Miller[26] seems to rule out a direct antagonism to vasopressin.

If Greenhill and Freed's[10] concept is correct that most, if not all, of the symptoms of premenstrual tension are the result of sodium and water retention, then not only are the breast, gastrointestinal, and pelvic manifestations understandable but their relief from a preparation like the one presently used should

be expected. On this same basis, it is surprising that headaches did not respond more satisfactorily.

Our present knowledge of the subject of premenstrual tension leaves much to be desired. Nevertheless, we believe agents capable of furthering the excretion of salt and water afford us a therapeutic step in the right direction. The present mixture of a theophyllinate and an antihistamine drug is the most satisfactory combination we have as yet used. The complete failures are still too common and indicate our lack of knowledge about the mechanisms concerned in the production of this interesting but baffling condition.

Summary and Conclusions

1. Of 43 patients with severe "premenstrual tension," clinically recognizable retention of water was present in 29, of whom 21, or 72.5 per cent, were definitely relieved by the use of a theophylline-antihistamine combination (neoBromth).

2. Therapeutic dosages ranged from 2 tablets (160 mg.) twice to four times daily for from 3 to 10 days prior to the onset of menstruation. In 3 instances continuous administration proved advisable.

3. No side effects were associated with the use of these doses.

4. It is concluded that the particular theophylline-antihistamine combination employed is a useful aid in the management of premenstrual tension, particularly when associated with high degrees of water retention.

References

1. Ellis, H.: Man and Woman, a Study of Secondary and Tertiary Sexual Characters, Boston, 1929, Houghton Mifflin Company.
2. Hoskins, R. G.: The Tides of Life, New York, 1941, W. W. Norton & Company, Inc.
3. Smith, G. van S.: In Williams, R. H.: Textbook of Endocrinology, Philadelphia, 1950, W. B. Saunders Company, p. 403.
4. Frank, R. T.: Arch. Neurol. & Psychiat. **26**: 1053, 1931.
5. Bickers, W.: South. M. J. **36**: 192, 1943.
6. Thorn, G. W., Nelson, K. R., and Thorn, D. W.: Endocrinology **22**: 155, 1938.
7. Hamblen, E. C.: Endocrinology of Woman, Springfield, Ill., 1945, Charles C Thomas, Publisher, p. 470.
8. Greenblatt, R. B.: Office Endocrinology, ed. 4, Springfield, Ill., 1952, Charles C Thomas, Publisher, p. 229.
9. Greenhill, J. P., and Freed, S. C.: Endocrinology **26**: 529, 1940.
10. Greenhill, J. P., and Freed, S. C.: J. A. M. A. **117**: 504, 1941.
11. Israel, S. L.: J. A. M. A. **110**: 1721, 1938.
12. Gillman, J.: J. Clin. Endocrinol. **2**: 157, 1942.
13. Freed, S. C.: J. A. M. A. **127**: 377, 1945.
14. Guterman, H. S.: J. Clin. Endocrinol. **10**: 641, 1950.
15. Harding, F. E.: Am. J. Obst. & Gynec. **50**: 56, 1945.
16. Freed, S. C.: J. Clin. Endocrinol. **6**: 571, 1946.
17. Taylor, H. C., Warner, R. C., and Welch, C. H.: Am. J. Obst. & Gynec. **38**: 748, 1939.
18. Bickers, W., and Woods, M.: New England J. Med. **245**: 453, 1951.
19. Grote, I. W.: Personal communication.
20. Bickers, W., and Woods, M.: Texas Rep. Biol. & Med. **9**: 406, 1951.
21. Bickers, W.: Am. J. Obst. & Gynec. **64**: 587, 1952.
22. Bickers, W., and Woods, M.: Am. J. Nursing **52**: 1087, 1952.
23. Vainder, M.: Indust. Med. **20**: 199, 1951.
24. Jones, H. E.: J. Tennessee M. A. **45**: 221, 1952.
25. Gibbs, O. S.: Personal communication.
26. Miller, G. E.: Personal communication.
27. McGavack, T. H., Pearson, S., and Haar, H.: Unpublished data.

Department of Case Reports New Instruments, Etc.

BILATERAL LIGATION OF THE COMMON ILIAC VEIN AT THE TIME OF CESAREAN SECTION

ROBERT W. KISTNER, M.D., AND CHRISTOPHER J. DUNCAN, M.D., BROOKLINE, MASS.

(From the Department of Obstetrics, St. Elizabeth's Hospital, Boston, and the Free Hospital for Women, Brookline, and the Department of Gynecology, Harvard Medical School, Boston, Mass.)

LIGATION of the inferior vena cava during pregnancy or at the time of parturition has been infrequently reported. Young and Derbyshire[10] reviewed the literature in 1950 and were able to cite only one previous case. In this patient, reported by Del Pino and Masciotra,[4] cava ligation was performed during the seventh month of pregnancy. Premature labor occurred on the following day, and the infant died neonatally. The postoperative course of this patient is not available for analysis.

The patient reported by Young and Derbyshire was a 21-year-old primigravida who had an appendectomy performed during the tenth week of pregnancy. Unilateral iliofemoral thrombosis occurred on the twelfth postoperative day and ligation of the inferior vena cava together with regional sympathetic blockade was promptly done. The immediate convalescence was uneventful except for moderate unilateral leg pain. Her subsequent pregnancy was uncomplicated. Labor began spontaneously at 39 weeks and a normal infant was delivered after 8 hours. The placenta appeared normal, there being no evidence of premature separation. Except for transient leg pain, the puerperium was uneventful. Uterine involution did not seem to be delayed. Examination 12 months following cava ligation showed both extremities to be normal.

Vells[9] reviewed the literature in 1952 and was unable to find a case wherein inferior vena cava ligation was performed in late pregnancy. This author reported the case of a 28-year-old primigravida who developed phlebothrombosis of the left lower leg with subsequent pulmonary emboli during the sixteenth week of pregnancy. A swollen left iliofemoral vein was palpable. The inferior vena cava was ligated below the level of the renal veins during the sixth month. Heparin was administered after the sixth postoperative day and ambulation was begun on the tenth day. She was discharged 4 days later. The pregnancy progressed favorably, no leg edema being noted even during the period of ambulation. During the eighth month of gestation she noted pain in the left iliac fossa for which heparin was given with relief of symptoms. A normal pelvic delivery was accomplished at term. There was no evidence of premature separation of the placenta and involution of the uterus was normal. Heparinization was maintained during the puerperium and five months post partum she was perfectly well without pain or edema.

Collins[3] and others[1, 5, 6] have reported normal pregnancies (a total of 9) and deliveries occurring subsequent to vena cava ligation. No apparent ill effects from previous surgery were evidenced during these pregnancies.

As far as can be determined from the literature, the following case is the first in which bilateral ligation of the common iliac vein was performed at the time of cesarean section. This ligation was physiologically and therapeutically equivalent to a cava ligation, but, because of technical variations, the iliacs rather than the cava were interrupted. It is because of this rarity that the following case report is cited:

This patient, a 22-year-old white para i, gravida ii, a physician, was first seen on June 29, 1954, because of acute chest pain of 4 days' duration. At this time she was in the thirty-fourth week of gestation, her last menstrual period having been on Nov. 3, 1953. She had noted sharp, excruciating pain in the right lateral chest which was aggravated by deep breathing and was associated with cough and blood-tinged sputum. The family history was relevant in that the patient's mother had died at the age of 38 years because of rheumatic heart disease. Her father, a diabetic, died at 58 years, apparently of a brain tumor. She had had scarlet fever and probable rheumatic fever during childhood, but gave no history of cardiac abnormality or decompensation.

A cesarean section had been performed in another city during the thirty-fifth week of her first pregnancy in 1951 for abruptio placentae, a 4 pound, 3 ounce infant being delivered. This infant survived and is living and well. A right phlebothrombosis occurred during the immediate puerperium, but pulmonary embolism was not evident until 9 months post partum. At this time anticoagulant therapy (heparin and Dicumarol) was initiated. Because of intermittent, recurrent pulmonary embolization, Dicumarol was administered from September, 1952, until March, 1954 (150 mg. of Dicumarol was given daily to keep the prothrombin time between 32 and 35 seconds). In March, 1954, at which time she was 16 weeks pregnant and still taking Dicumarol, vaginal bleeding was noted. Dicumarol was then discontinued and had not been restarted during this pregnancy.

Physical examination showed a well-developed, apprehensive white woman. The pulse was 92, temperature 99.2° F., respirations 24. The serologic test for syphilis was negative. She was Rh positive, group A. The urinalysis was normal. The heart was normal in size, the rhythm regular, and no murmurs were heard. Auscultation of the chest was normal. The size of the uterus was consistent with a 34 weeks' pregnancy, the fetal heart being heard in the right lower abdominal quadrant.

The possibility of a recurrent pulmonary infarct was considered and an immediate chest x-ray was ordered. This was negative. Four days later the patient telephoned that she had had another bout of chest pain. She was admitted to the hospital immediately.

Physical examination at the time of entry to the obstetrical service on June 30, 1954, showed: pulse 88, temperature 99.0° F., respirations 18. The heart was of normal size, the rhythm regular, and no murmurs were heard. A friction rub was audible in the right chest in the mid-axillary line at the fifth interspace. The uterine fundus was enlarged to 4 cm. below the ziphoid, with a vertex presentation, floating over the inlet of the pelvis. The fetal heart rate was 140. There was minimal tenderness in the right calf posteriorly, but Homans sign was negative. The electrocardiogram showed: "right axis deviation with S_1, Q_3—can be seen in pulmonary infarctions." X-ray of the chest showed normal heart and lungs. The hemoglobin was 12.4 Gm.; the white blood count 13,700 with a normal differential.

A diagnosis of recurrent pulmonary infarction with an intrauterine gestation of 35 weeks was made. She was given Pantopon, ⅓ grain, and heparin concentrate, 100 mg. (100 mg. per cubic centimeter). Ligation of the inferior cava was considered as optimum treatment, but in view of the technical difficulties associated with a uterus of this size, it was decided to use anticoagulants until the time of cesarean section and then ligate the

cava. Since Dicumarol is known to pass the placental barrier and enter the fetal circulation and since heparin does not present this disadvantage, it was planned to continue full heparinization up until the time of operation. Accordingly, heparin was given in a dose of 100 mg. every 8 hours (intramuscularly) unless the coagulation time exceeded 20 minutes. After 72 hours of treatment the patient was allowed out of bed and heparin continued every 12 hours. Protamine sulfate and a syringe for its use were kept at her bedside constantly in case of sudden bleeding or initiation of labor. After 48 hours the chest pain and hemoptysis subsided, but a repeat electrocardiogram was interpreted as "consistent with pulmonary infarction." Heparin treatment was continued until July 13, 1954, at which time the gestation approximated 37 weeks. Heparin was omitted on that day and on July 14, 1954, a low transverse cervical cesarean section was done under spinal anesthesia. The clotting time just prior to operation was 7 minutes. A living female infant weighing 4 pounds, 10 ounces was delivered without incident. The uterus was then closed and lifted anteriorly. The posterior peritoneum was opened and both common iliac veins mobilized to their junction to form the cava. It seemed technically easier to ligate both common vessels just at their entrance into the cava and this was accomplished with double ties of No. 3 silk. The posterior peritoneum was closed and the uterus observed for several minutes. It did not change in color, size, or consistency. The infundibulopelvic veins were not ligated. No evidence of pelvic, iliac, or femoral phlebothrombosis was evident. The abdomen was then closed in the usual fashion.

The patient was placed in bed with both legs elevated and wrapped snugly in Ace bandages. Heparin was restarted 12 hours after operation in the same dosage as had been carried out preoperatively. A continuous intravenous infusion of Pitocin in 5 per cent glucose in water was given slowly for 24 hours. There was no excess vaginal bleeding and ambulation was begun on the second postoperative day. She was not permitted to sit, but either walked about the room or remained in bed with legs elevated. On the seventh day heparin was discontinued and anticoagulation continued with Hedulin* (2-phenylindane-1,3-dione), the dosage being regulated to keep the prothrombin time between 30 and 35 seconds.

Convalescence was afebrile and uneventful except for severe and at times excruciating deep pelvic pain. There was no leg pain or edema. Sutures were removed on the seventh day and the patient was discharged on the twelfth postoperative day in good condition except for continued pelvic pain. She continued to take Hedulin (50 mg. every 12 hours) for 3 weeks postoperatively. The infant was discharged living and well when the birth weight reached 5 pounds, 10 ounces.

An examination on Aug. 9, 1954, showed slight edema of the right ankle, pretibial area, and thigh. This had its onset about 3 weeks after the ligation. She was feeling well and there had been no recurrence of chest pain. The uterus was anterior, of normal size, and well involuted. Examination of the sides of the pelvis and rectum was negative.

Seven months postoperatively (Feb. 18, 1955) there was minimal edema of both ankles and lower legs and moderate edema of the distal one-third of the right thigh. She had noted rather massive edema of the right thigh in late August, 1954, but this subsided after 16 hours' ambulation. An episode of acute phlebitis involving the superficial femoral system of the left leg occurred in October, 1954. This cleared without residual edema.

There was no pelvic or leg pain as of February, 1956, and only a slight increase in the superficial collateral circulation of both thighs. She had noted no leg weakness and was not conscious of fatigue. Menstrual periods had been normal in amount, duration, and interval without dysmenorrhea. She was engaged in full-time medical practice and was able to work without restriction.

Comment

The management of this patient presented, at the outset, several problems. Because of recurrent pulmonary embolism and in view of her past history of thromboembolic disease, the optimum treatment appeared to be immediate

*Walker Laboratories, Inc., Mount Vernon, N. Y.

ligation of the inferior vena cava. Despite the fact that there are three cases on record in which the cava was ligated during pregnancy without obvious deleterious effect, the recent work of Mengert[8] in which caval obstruction was implicated in the etiology of abruptio placentae was considered in reaching a decision. Therefore, anticoagulation utilizing heparin was instituted and the patient was fully heparinized up until the time of cesarean section.

From available data it may be assumed that heparin does not pass the placental barrier and thus has no effect on the coagulation time of fetal blood. Dicumarol, however, readily traverses the placenta and enters the fetal circulation. Several reports have cited cases of intracranial and intrapulmonary hemorrhage following prolonged Dicumarol administration. During the prenatal stage, then, it seems safer to utilize heparin when anticoagulants are indicated. Heparin should be utilized in full and adequate dosage, Jorpes[7] having suggested a daily minimum of 300 mg.

Ligation of the cava or bilateral ligation of the common iliac veins at the time of cesarean section is not difficult technically. The uterus may be easily displaced forward and held out of the operative field by curved retractors. Both common iliac veins are readily accessible for mobilization and ligation. The lower cava is somewhat more difficult to mobilize, but ligation is not difficult.

Postoperatively anticoagulant measures should be reinstituted, with heparin followed by either Dicumarol, Coumadin, or Hedulin. A continuous intravenous infusion of Pitocin may be utilized during the early postoperative period of heparinization to maintain uterine tone and diminish bleeding. Both legs should be snugly wrapped in Ace bandages and ambulation on the first day accomplished.

Cava ligation and simultaneous ovarian vessel ligation do not materially alter the normal cyclic physiological processes of the uterus and ovaries. Studies by Collins and associates[3] have shown uterine bleeding of normal duration and amount in the vast majority of their patients. They presented evidence of ovulation in 29 patients subsequent to ligation as determined by pregnancy, secretory endometrium, or corpora lutea.

Ligation of the inferior vena cava has long been held in disrepute because of incapacitating edema of the leg, ulceration of extremities, or chronic fatigue. Recent reports, however, indicate that this viewpoint has been overly pessimistic. The patients operated upon by Collins and his group have, for the most part, been young-to-middle-aged women. Ligation was not done during pregnancy, but was carried out in most instances because of septic postabortal emboli. Their results may be classified as excellent. At the Free Hospital for Women 5 ligations of the cava were performed during the interval 1943–1953. Two of these were done for phlebothrombosis without embolism and 3 for nonfatal pulmonary emboli. Two of these patients reported moderate persistent edema whereas 3 noted only intermittent edema which was not bothersome. Skin ulceration did not occur and, while activities were somewhat curtailed, fatigue was not excessive.

The absence of leg edema following the 2 ligations performed during pregnancy and the minimal edema noted in our case suggest that the extensive venous collateral circulation associated with pregnancy diminishes the morbidity of this procedure if carried out either during pregnancy or at the time of delivery.

References

1. Burke, L., and Rosenfeld, H. H.: AM. J. OBST. & GYNEC. **64**: 694, 1952.
2. Collins, C. G., et al.: AM. J. OBST. & GYNEC. **58**: 1155, 1949.
3. Collins, C. G., et al.: AM. J. OBST. & GYNEC. **63**: 351, 1952.
4. Del Pino, P., and Masciotra, R. L.: Semana méd. **36**: 1632, 1929. (Quoted by Foulkes.[5])
5. Foulkes, J. F.: J. Obst. & Gynaec. Brit. Emp. **55**: 798, 1948.
6. Heath, L. P., and Carpenter, W. S.: AM. J. OBST. & GYNEC. **64**: 692, 1952.
7. Jorpes, J. E.: Acta chir. scandinav., 1950, supp. 149.
8. Mengert, W. F., et al.: AM. J. OBST. & GYNEC. **66**: 1104, 1953.
9. Vells, Serra J.: Angiologia **4**: 235, 1952.
10. Young, R. L., and Derbyshire, R. C.: Ann. Surg. **131**: 252, 1950.

MASSIVE THROMBOPHLEBITIS OF THE OVARIAN VEIN

A Case Report

O. G. Austin, M.D., Medina, Ohio

(From the Obstetrical Department, Medina Community Hospital)

A CASE is here reported to illustrate another of the many thrombotic phenomena associated with pregnancy. The extent of the process, the efficiency of collateral circulation, and the successful outcome of surgery appear to warrant the report.

Hodgkinson's[1] work has shown that with the tremendous dilatation of the ovarian vein during pregnancy its capacity may be increased sixty fold. The hypertrophy of smooth muscle in the media of the vein apparently acts as a protective mechanism to withstand the additional load of pregnancy. The gross and microscopic findings of the following case are in accord with this description.

A 22-year-old Negro girl had had her second delivery two days before being seen on consultation. Unrecognized twins had been born, one living, the other, macerated, had apparently been dead for several weeks. The attending physician requested consultation because of increasing pain in the right lower quadrant radiating to the right side of the back and the area of the right costovertebral angle. A few hours before examination she had begun to vomit and had retched nearly constantly since that time. Now the patient described the pain as being much less in the back and more localized to the right lower abdomen.

A catheterized urine specimen was negative, the white blood count was 9,000, with a normal distribution of white cells, and the red blood count was 3½ million, with 70 per cent hemoglobin. On examination, a postpartum fundus could be felt just below the umbilicus. The abdomen was flaccid and the patient was quite thin, making abdominal palpation easy. A mass could be felt on the right side of the uterus near the cornu, definitely attached to the uterus. This mass could not be well outlined because of the extreme tenderness and because of spasm of the rectus muscle at this level. There was rebound tenderness over the mass, and referred from the left lower quadrant to the location of the mass. No abdominal distention was present and the lochia appeared to be normal for a patient forty-eight hours postpartum. There was only slight residual tenderness over the right kidney area, but it was felt that an intravenous pyelogram should be done to rule out renal or ureteral pathology. The symptoms of pain and vomiting became progressively more severe and during the evening about six hours after the patient was first seen it was decided to perform a laparotomy.

The following differential diagnoses were entertained: (1) acute appendicitis, and with the presence of a mass, probably ruptured. This diagnosis was considered despite the lack of fever or leukocytosis; (2) possible torsion of a right ovarian cyst; (3) pyosalpinx on the right. Other diagnoses considered to be more remote possibilities were hematoma in the broad ligament or degeneration of a fibroid. The delivery itself had been easy and spontaneous and it was not felt that the uterus was ruptured. A consultation with a general surgeon was held and he was in accordance with the decision to open the abdomen.

Laparotomy was performed under ether anesthesia through a right rectus incision over the previously described mass. Upon opening of the abdomen there was only a small quantity of straw-colored fluid present. The mass was immediately seen to be lying in the broad

ligament and apparently was clotted blood. Examination of the remainder of the abdomen showed that along the course of the right ovarian vein, from the broad ligament to the infundibulopelvic ligament and upward, the vein was tremendously enlarged, averaging 2 inches in diameter, and filled with clots which were quite firm. At the level of the broad ligament, the thrombotic mass was the size of a large orange. An incision was made through the broad ligament and into the mass with the idea of emptying the clotted material. As the clots were aspirated and wiped out of the cavity, the lining of the cavity could be seen as a distinct wall and, in some areas, valvular structures could be seen. Therefore, we thought we were dealing with intravascular clotting, rather than a hematoma per se.

The clot was not well organized and in some areas could be removed with suction. The great bulk of the clotted blood, however, was removed by expressing the blood manually through the incision, which opened the anterior leaf of the broad ligament and the wall of the vein. The right tube and ovary, which were of normal appearance, were removed. It was decided to try to evacuate the entire clot. Consequently, dissection along the ovarian vein was begun and was carried out through the infundibulopelvic ligament and to the level of the kidney, on the right side. The diameter of the ovarian vein measured here from 1 to 2 inches and, in some areas, the varicosities ballooned upward during the dissection resembling very much the blood-filled simple cysts so often seen in the ovary. Palpation of the vein as far as its anastomosis with the inferior vena cava showed that the clot extended into the vena cava and continuing upward could be felt as far as the opening of the diaphragm. Accordingly the ovarian vein was tied with silk at the anastomosis with the vena cava and the vena cava was ligated just below the entrance of the right renal vein. It was felt that, with the clot extending as high as the diaphragm, the situation was desperate. The entire ovarian vein was extirpated.

The patient stood the procedure fairly well and was given 500 c.c. of blood during the operation. She left the operating room in fairly good condition to receive anticoagulants.

Microscopically, the diagnosis was acute thrombophlebitis, the wall of the vein being infiltrated with neutrophilic leukocytes and a few lymphocytes.

Six weeks later, under local anesthesia plus intravenous Pentothal, the remaining tube was removed. Elective sterilization was considered to be necessary in the patient as her psychological make-up made other means of contraception quite hazardous.

The left broad ligament, tube, and ovary with associated vessels seemed normal. On the right there was no obvious dilatation of the veins remaining in the broad ligament. The cecum was adherent to the broad ligament and to the parietal peritoneum at the site of our dissection and was not disturbed.

Examination of the patient four months after the first operation failed to show any evidence of distention of superficial veins in the upper or lower portions of her body. Kidney function has remained normal; she concentrates urine well and has no renal pain.

One must only marvel at the efficiency of the collateral collecting system and postulate that the canal remaining in the inferior vena cava has been adequate. It is difficult to say whether the situation arose from a congenital or an acquired phlebectasia.

Reference

1. Hodgkinson, C. P.: Obst. & Gynec. 1: 26, 1953.

A CASE OF INTERSTITIAL TUBAL PREGNANCY WITH RUPTURE INTO THE BOWEL*

AUGUSTA WEBSTER, M.D., AND CHARLOTTE HERMAN KERR, M.D., CHICAGO, ILL.

(From the Department of Obstetrics, Cook County Hospital, and the Department of Obstetrics and Gynecology, Northwestern University Medical School)

MRS. L. J. (No. 52-13416), a 38-year-old Negro housewife, gravida iv, para iii, was first admitted to the Cook County Hospital March 10, 1952, with the complaint of cramping pains in the suprapubic area and in the back, associated with the passage of large blood clots from the vagina for three days. The pain and bleeding continued until the day of admission, when chills and nausea were also noted. Her last normal menstrual period was Jan. 21, 1952 (six and one-half weeks before admission). February 22 she had a scanty flow for two days only. Her previous menstrual periods had been normal and regular. Her past history was noncontributory.

General physical examination was normal except the lower abdomen. Bowel sounds were normal. There was slight suprapubic tenderness. No abdominal masses were made out. On speculum examination a large cervix was seen with no active bleeding. Bimanual examination disclosed a soft, closed cervix. The corpus was the size of a fourteen weeks' pregnancy. Adnexa and cul-de-sac were negative. Her temperature was 100.4° F., pulse 120, respirations 18, and blood pressure 120/70. The impression was that of a threatened abortion.

The hemoglobin was 85 per cent; urinalysis including microscopic examination was negative.

Treatment consisted of penicillin and sulfadiazine for three days. The day after admission she became afebrile, but two days later her temperature rose to 101° F. and her pulse to 120. Medication was then changed to streptomycin which she received for two days, and she again became afebrile.

Slight vaginal bleeding was noted for only two days after admission. She became asymptomatic on March 14, four days after admission, and was discharged the following day with a diagnosis of threatened abortion.

The patient was readmitted to the Cook County Hospital April 10, 1952, three and one-half weeks after discharge from the hospital. She complained chiefly of weakness rather than pain since March 15. For one week prior to readmission she had noticed occasional pain in the lower back, right groin, and down the right leg from the knee to the foot. On April 6 she awoke with a shaking chill which lasted half an hour, followed by fever and perspiration. After the chill she noted a constant burning pain in the right lower abdominal quadrant which did not radiate. For the next two days she had no appetite and was drowsy. On April 9 (one day before admission) the pain in the right lower quadrant recurred, but was never enough to require bed rest. That afternoon she had two bowel movements containing blood. Up to that day the bowel movements had been normal. That night she experienced another shaking chill, vomited, and felt weak. She had two more liquid stools containing blood. On April 10, the day of admission, she was dizzy, felt faint several times, and had four liquid stools containing blood.

Physical examination showed a very pale Negro woman in moderate abdominal distress. Her temperature was 100° F., pulse 116, and blood pressure 110/60. The abnormal physical findings were confined to the abdomen and pelvis. The abdomen was soft with a slightly tender, palpable mass the size of a fist in the right lower quadrant. Bowel

*Presented at a clinical meeting of the Chicago Gynecological Society, Jan. 21, 1955.

sounds were normal. The cervix was soft, movable without pain, pale, and the external os was closed. Hegar's sign was positive. The corpus was soft, anterior, and questionably enlarged to the size of an eight to ten weeks' pregnancy. In the right adnexa was a soft, slightly tender mass with indistinct borders that extended to the right anterior iliac spine, and was freely movable. The left adnexa and cul-de-sac were negative. Rectovaginal examination confirmed these findings and showed dark blood in the rectum.

On the day of admission, April 10, a proctoscope was passed to 15 cm. and no lesions were found. The instrument could not be passed further because of large clots of blood. The blood count was: erythrocytes 1.51 million; hemoglobin 25 per cent; leukocytes 14,200; sedimentation rate 13 mm.; and hematocrit 16 per cent. Urinalysis was negative. She received 2 pints of blood and the day after admission the blood count was; erythrocytes 2.42 million; leukocytes 22,650, hemoglobin 34 per cent, and the platelets 425,900. The differential count showed 61 per cent polymorphonuclear leukocytes, 28 per cent neutrophil bands, 8 per cent lymphocytes, and 1 per cent monocytes.

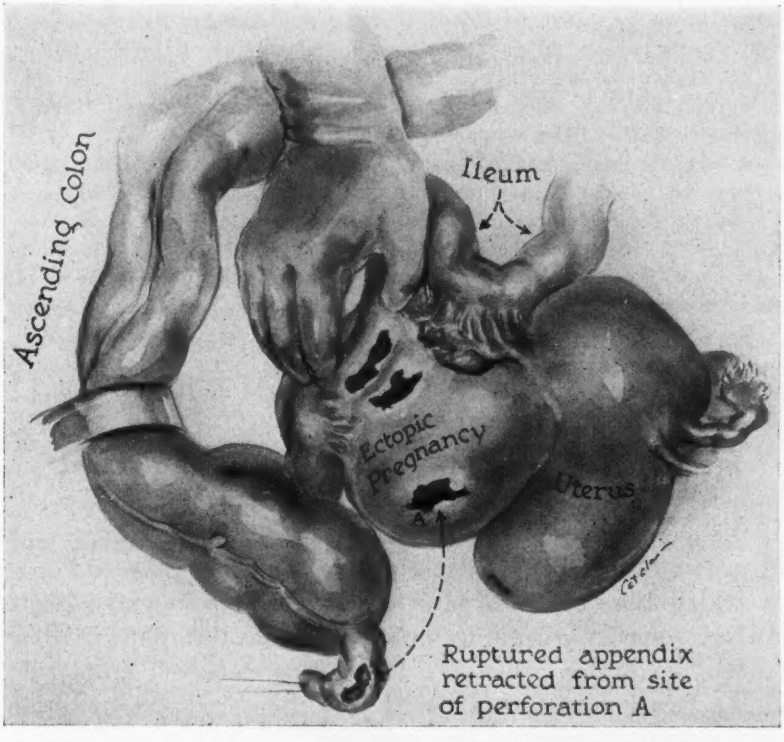


Fig. 1.—Shows relative positions of ectopic pregnancy, appendix, and ileum.

She was given analgesia for the continuous pain in the right lower quadrant, antibiotics, and on April 12 again received 2 pints of blood. She had five loose black bowel movements during the night but no bright red blood was seen. On April 12, the temperature was 100° F., pulse 124, and blood pressure 104/70. The abdomen was less tender. Levine suction was instituted to determine if there were any blood in the upper gastrointestinal tract, but none was returned through the suction.

Medical and surgical consultations were obtained. Carcinoma of the cecum was strongly suspected but no one was willing to introduce barium into the bowel for diagnosis. On April 13, it was agreed that a laparotomy was indicated. The patient had received 4 pints of blood up to this date and the hemoglobin was 8 Gm. per 100 ml. blood, and the red cell count was 2.7 million. She then received 8 additional pints of blood in preparation for operation.

Laparotomy on April 14 showed a ruptured right interstitial tubal pregnancy which had been walled off by the cecum, appendix, and terminal ileum. A large erosion about one and one-half inches in width had produced an opening into the terminal portion of the appendix and another into the ileum about 4 inches from the ileocecal valve (see Fig. 1 which is a composite of several photographs taken at the time of operation). There was no free blood in the peritoneal cavity. Much edema was present around the walling-off process. As the component parts of the mass were separated, considerable decidua-like tissue was encountered. The interstitial portion of the right tube and cornu of the uterus were removed in a wedge. The appendix was removed retrograde. About 3 inches of terminal ileum was resected and an end-to-end anastomosis was performed about 1½ inches from the ileocecal valve by the general surgeon called in consultation.

The patient received 4 pints of blood during operation and had a mild transfusion reaction on leaving the operating room, but seemed to be in good condition that evening. She was given antibiotics, vitamin K, sedatives, and intravenous fluids, and Levine suction was instituted.

Her temperature was 102° to 102.6° F. for the first three postoperative days. Her bowels moved spontaneously on the third postoperative day, but the abdomen was distended and bowel sounds were hypoactive. Aureomycin was then ordered to replace penicillin and streptomycin. She developed atelectasis in the right lower lobe on the fourth postoperative day and her temperature rose to 105° F.

Jaundice was observed on the fourth postoperative day and blood studies showed the icterus index to be 100, total protein 5.9 Gm. per cent, chloride 102 meq. per liter, sodium 134 meq. per liter, potassium 18.7 mg. per 100 c.c., and carbon dioxide combining power 38 volumes per cent. A blood count showed 94 per cent hemoglobin and 6,500 leukocytes. A chest x-ray the same day showed the left lung field to be essentially clear with ill-defined areas of increased density in the right base, interpreted as pneumonia or atelectasis. By 4 P.M. on the fourth postoperative day her temperature was 106° F., and at 4:45 P.M. the same day she died.

The pathologist reported chorionic villi diagnostic of a tubal pregnancy in the surgical specimen. Permission for postmortem was refused.

It is regrettable that an earlier correct diagnosis was not made. The patient's stoicism and indifference to pain were misleading. In retrospect one wonders if the diagnosis of interstitial pregnancy might have been made had the patient presented herself for examination one week prior to her second admission, at which time she felt pain in the right groin and right leg. One might also conjecture as to whether or not the patient might have lived had an ileostomy been performed when the lesion was removed from the terminal ileum, and the bowel anastomosis delayed until her general condition was improved and the decidual reaction had subsided.

We are reporting this case because of certain misleading factors in the history and findings. Erosion of an ectopic pregnancy into the bowel is rare. In a review of over one thousand consecutive ectopic pregnancies at the Cook County Hospital since 1940 this is the only instance of bowel invasion.

ECTOPIC PREGNANCY FOLLOWED BY TWO RECURRENCES

A Case Report

HENRY B. TURNER, M.D., AND T. MURRAY FERGUSON, M.D., MEMPHIS, TENN.

(From the Division of Obstetrics and Gynecology, University of Tennessee College of Medicine and the City of Memphis Hospitals)

A SECOND or recurrent tubal pregnancy in the same patient is occasionally encountered. The recurrence of this condition twice after the initial episode is extremely rare. Indeed, the extent of surgery will most often preclude further pregnancy following treatment of the second tubal gestation. With the advent of refinements in plastic procedures of the tubes, however, including the use of polyethylene tubing, the possibility of recurrent eccyesis in increasing numbers becomes more likely.

A review of the recent literature discloses frequent reports of one recurrent tubal gestation, usually in the opposite tube. Several articles report recurrent involvement on the same side, the second pregnancy most often being of the interstitial type.[1-5] Reference to cases of 3 tubal pregnancies in the same woman has been made by Duca[6] and, most recently, by Marbach and Schinfeld.[7] Apparently, only 8 such cases have been previously reported, the case herein discussed being the ninth.

Our patient, a 29-year-old Negro woman, was seen first in the outpatient department of the City of Memphis Hospitals on June 23, 1953. She was para iii, abortus ii, and gave the history of previous right salpingo-oophorectomy for a ruptured tubal pregnancy in 1950 in another hospital. Her last normal menstrual period was May 3, 1953. She had spotted scantily about one week previously and 12 hours prior to her clinic visit she had a sudden sharp lower abdominal pain of short duration and passed a piece of tissue which she brought to the clinic. Upon inspection this was obviously a decidual cast of the uterus and pathological examination confirmed that impression. Examination showed a small amount of dark blood coming from the cervical os but no masses were palpable. There was no tenderness, and the softened uterus was the only suggestion of pregnancy. Colpocentesis was negative. She was admitted to the hospital and on June 26, 1953, a culdoscopic examination was done. As suspected, a small unruptured pregnancy was seen in the left tube. On June 29, 1953, under general anesthesia an exploratory laparotomy was performed. The tubal pregnancy was visualized about 3 cm. from the uterine cornu. A dorsal slit was made in the tube and the pregnancy gently expressed. Bleeding was slight. The tube was probed for patency proximally and distally, and then closed with fine gastrointestinal interrupted sutures. After an uneventful postoperative course the patient was discharged on the sixth day.

On April 13, 1955, about 9 P.M. this patient came to the emergency room complaining of lower abdominal pain and vaginal bleeding. Her periods had been regular and normal following the previously described illness until Feb. 15, 1955, when she noted spotting for 2 days at the time of her regular period. She missed her March period entirely but bled a small amount painlessly on April 9, 1955. On April 12, 1955, she began slight bleeding again and

about 6 P.M., April 13, 1955, passed some tissue with mild cramping pain. The tissue upon examination again appeared to be a decidual cast. The lower abdomen was tender and a 3 cm. mass was palpable in the left adnexal area. Colpocentesis was negative. A tentative diagnosis of unruptured left tubal pregnancy was made. Pathological examination of the tissue confirmed the impression of decidual cast. On April 14, 1955, culdoscopy was done and a 3 cm. mass resembling a tubal pregnancy was visualized in the left tube. On April 15, 1955, exploratory laparotomy was done under spinal anesthesia. Inspection confirmed the impression of left tubal pregnancy. A left salpingectomy and total hysterectomy were performed. The postoperative course was uneventful. Routine laboratory studies at each admission were normal. The pathological report on each of the two specimens confirmed the presence of tubal gestation.

Eastman[8] stated that following tubal pregnancy only about one woman in three will again conceive. Of these, the likelihood of another tubal pregnancy occurring is one in ten. Most often this recurrence is in the opposite tube but infrequently the stump of the same tube is involved. Rarest of reported cases is the occurrence of three tubal gestations in the same person. The case herein reported is even more unusual in that in the second and third tubal gestations diagnosis was possible by culdoscopy prior to rupture.

It has been suggested that tubal insufflation following the second operation might have decreased the likelihood of a third tubal pregnancy. Should such an opportunity present itself again it is our intention to carry out that procedure.

Summary

A case has been reported in which the same patient experienced three tubal pregnancies within a period of five years. The last two incidents of eccyesis were unruptured at the time of operation. To our knowledge, no similar case has been reported previously and only eight cases could be found in which tubal gestation has occurred three times.

References

1. Lingenfeld, J.: U. S. Armed Forces M. J. 1: 550, 1950.
2. Ganther, J.: Union méd. Canada 79: 1444, 1950.
3. Gee, S.: Brit. M. J. 1: 841, 1945.
4. Bryan, H., and Montemuro, T. J.: Canad. M. A. J. 55: 601, 1946.
5. Lee, A. F.: Northwest Med. 46: 535, 1947.
6. Duca, A.: Riv. d'ostet e ginec. prat. 29: 294, 1947.
7. Marbach, A. H., and Schinfeld, L. H.: AM. J. OBST. & GYNEC. 62: 1376, 1951.
8. Eastman, N. J.: Williams Obstetrics, ed. 10, New York, 1950, Appleton-Century-Crofts, Inc.

DEATHS OF TWO CONSECUTIVE INFANTS BORN OF A MYASTHENIC MOTHER*

ALEX J. ARIEFF, M.D., AND W. R. ROACH, M.D., CHICAGO, ILL.

(From Northwestern University Medical School and Passavant Memorial Hospital)

PREGNANCY in women with myasthenia gravis is rare. Wilson and Barr, quoted by Bryan,[2] found one such patient in 63,268 admissions from 1900 to 1940 at the Boston Lying-in Hospital. Viets and associates[3] found that pregnancy usually decreased symptoms even up to a remission (8 cases). Levin[6] divided symptoms of myasthenia after birth into the neonatal type in infants born of a myasthenic mother and congenital myasthenia in infants having a normal mother. Stickroot's[4] infant had neonatal myasthenia and died one week after birth, which is a long time to develop symptoms. (This could have been a congenital case.) The infant in Bryan's[2] case developed symptoms the day after birth and survived on Prostigmin therapy, showing no symptoms eight months later, although the mother died eight months post partum in a myasthenic crisis.

Our report is as follows:

M. D., a 32-year-old woman, was first seen in February, 1939, when she was 18 years of age. She developed symptoms of myasthenia at the age of 16: Her weakness was mainly in the jaws, face, tongue, and palate, least of all in the extremities. Her weakness was not classic in that it was worse early in the morning. She was one of seven siblings. The family history was unusual in that one sister died of a pituitary tumor even after "successful" surgery. One brother had "glandular trouble." Her mother developed thyrotoxicosis and one sister and an aunt had amenorrhea.

Under Prostigmin therapy she had a classic remission but before the next dose was administered she would be weaker than before the treatment. This effect made her fear taking the Prostigmin. After a few months under my care (A. J. A.) she finally did well on a combination of eight 15 mg. tablets of Prostigmin, 3/50 grain eserine, and three 3/8 grain capsules of ephedrine per day. Her course fluctuated somewhat, but she was well enough to work in the family bakery shop and engage in limited social activities. A few times after an acute infection she developed an acute myasthenic bulbar paresis which necessitated Prostigmin by hypodermic injection. She kept a few ampules at home for emergency use. After a few years she developed diplopia which was very little affected by Prostigmin therapy. Other therapy included x-ray and other newer drugs without effect.

In 1949 at the age of 29 she married. Her husband understood she had a serious muscular illness and both were warned against having children. In July, 1951, she became pregnant. The pregnancy was uneventful. In June, 1952, after 40 weeks, she went into a normal labor, giving birth to a baby that appeared normal, and cried at once. Twelve hours later, however, the infant became cyanotic and was placed in an oxygen tent. Three hours later Prostigmin was given without effect and the infant died 28 hours after birth. Necropsy revealed an atelectatic lung. The mother felt weaker and diplopia was more severe.

*Presented at a meeting of the Chicago Gynecological Society, May 20, 1955.

Again against medical advice in November, 1952, she became pregnant. This baby was delivered on June 21, 1953, after an uneventful 40 weeks' pregnancy. The baby cried spontaneously but rapidly became cyanotic. It was breathing mainly abdominally and was placed in oxygen. Prostigmin was given five hours later without effect and the baby died six hours after birth. The pathologic report revealed passive hyperemia of the lungs, liver, and spleen with a patent ductus arteriosus. The mother developed a postpartum hemorrhage and died. Autopsy was refused.

There must be a moral in this, and that is, "Human nature is hard to change."

Walker[1] has summarized the literature on myasthenia in infants. In 17 infants born with myasthenic symptoms, 4 were from normal nonmyasthenic mothers and only one died. The mothers of the other 13 all had myasthenia and 2 infants died on the fourth and the sixth days. Prostigmin was helpful in some of the latter group. The important point is that the child born of a myasthenic mother may become normal if it lives through the acute period. Diagnosis must rule out amyotonia congenita which may simulate myasthenia in infancy. The Prostigmin test is definitely diagnostic. It may be postulated theoretically that the blood of the infants whose mothers had myasthenia had the "myasthenic factor." In myasthenic infants born of nonmyasthenic mothers, however, the child will have myasthenia and will need treatment specifically. In both cases, Prostigmin should be given immediately at birth before untoward symptoms occur. It is possible, also, that the replacement of the infants' blood by transfusion as is done in Rh incompatibility would help.

Summary and Conclusion

Two infants born of consecutive pregnancies of a myasthenic mother died twenty-eight and six hours after birth in spite of Prostigmin therapy. It is suggested that because such infants may become perfectly normal if they survive for a number of days, and that Prostigmin should be given immediately at birth. The possibility is mentioned that a complete exchange of blood, thereby eliminating the possible maternal "myasthenic factor," might save the lives of some infants.

References

1. Walker, Rhett P.: Am. J. Dis. Child. **86**: 198, 1953.
2. Bryan, W. M., Jr.: Obst. & Gynec. **4**: 339, 1954.
3. Viets, H. R., Schwab, R. S., and Brazier, M. A. B.: J. A. M. A. **119**: 236, 1942.
4. Stickroot, F. L., Schaeffer, R. L., and Birgo, H. L.: J. A. M. A. **120**: 1207, 1942.
5. Gans, B., and Forsdic, D. H.: Brit. M. J. **1**: 314, 1953.
6. Levin, P. M.: Arch. Neurol. & Psychiat. **62**: 745, 1949.

TUBERCULOUS MENINGITIS AND PREGNANCY*

Report of One Case

H. G. K. FAALAND, COMMANDER (MC)USN**

(From the Obstetrical and Gynecological Service, U. S. Naval Hospital, St. Albans, Long Island, N. Y.)

PULMONARY tuberculosis and pregnancy coexist in about 2 per cent of all pregnancies. Extrapulmonary tuberculosis was found to be present in 0.1 per cent of 67,232 pregnancies at New York Lying-In Hospital.[1] Miliary tuberculosis, which seems to precede most cases of meningitis, according to Lundström,[2] is associated with pregnancy with an incidence ranging from 0.04 to 1.2 per cent.

Tuberculous meningitis, because of its rarity, is seldom diagnosed during pregnancy. In cases reported in the literature, adequate treatment was usually first started between two and three weeks after onset of the illness. Kane,[3] Swift,[4] and Silverman and Feinblatt[5] each reported a case discovered early in pregnancy between 20 and 29 weeks' gestation, adequately treated with streptomycin, and followed by survival of mothers and infants. Rutberg[6] reported a case diagnosed at 19 weeks and treated with streptomycin and para-aminosalicylic acid with an excellent result. Downs and Clarke[7] reported upon a patient with tuberculosis in pregnancy who developed tuberculous meningitis at 7 months' gestation while under treatment in a sanatorium for chronic fibrocavernous pulmonary tuberculosis. Streptomycin therapy resulted in a normal full-term infant and recovery from the meningitis eight months post partum. Rogers, Wilson, and Goodier[8] reported a case of acute miliary tuberculosis and meningitis which developed at 32 weeks of pregnancy. The patient was treated with streptomycin without para-aminosalicylic acid for 4½ months. She delivered a normal infant but died within 3 months post partum. Faugère[9] described a case of tuberculous meningitis in which streptomycin therapy was started in the eighth month. The infant, delivered at term, died of tuberculous peritonitis 16 days after birth. Goodwin and Kenler[10] reported a case of miliary tuberculosis in pregnancy complicated by meningitis following temporary improvement under streptomycin therapy. After delivery the patient lapsed into coma and died 12 days post partum. The placenta showed gross and microscopic evidence of miliary tuberculosis. The infant was treated prophylactically with streptomycin and survived.

The prognosis for patients with tuberculous meningitis is indeed very poor. Silverman and Feinblatt[5] reviewed 66 cases of tuberculous meningitis

*Views, impressions and statements expressed in this article are those of the author and are in no way representative of the Medical Department of the U. S. Navy.

**Currently Chief of Dependents' Service, U. S. Naval Hospital, Jacksonville, Fla.

at Kings County Hospital, Brooklyn, New York, over a five-year period. Of 6 patients treated with streptomycin there was one survivor. Of 60 patients not treated with streptomycin there were no survivors. The average survival time in untreated cases was 15.6 days; in treated cases 66.8 days. Bunn[11] in a two-year follow-up of 81 patients with tuberculous meningitis with or without miliary tuberculosis and treated with streptomycin found only 10 survivors. Several of the latter had serious neurological sequelae. Fitzpatrick[12] reported the use of streptomycin, isoniazid, and para-aminosalicylic acid in 11 patients with tuberculous meningitis and predicted that a survival rate of about 50 per cent can be obtained by prolonged management with these drugs.

The obstetrical management of cases of this nature would necessarily be individualized. Beck[13] in 1939 stated that cesarean section has been recommended in the treatment of this complication. Rand and Andler[14] in their paper, "Tumors of the Brain Complicating Pregnancy," stated that they believed the strain of labor increases intracranial pressure, although they had no figures to prove it. They consequently advised cesarean section as safer than vaginal delivery for pregnant women harboring brain tumors. Should there be means of cerebral decompression present at the onset of labor as in the case to be presented, the major objection to vaginal delivery would then possibly be eliminated. In all the reported cases of tuberculous meningitis in pregnancy reviewed, delivery was accomplished vaginally.

One additional case is hereby reported.

K. M., a 31-year-old primigravida of Korean extraction, was admitted to U. S. Naval Hospital, St. Albans, New York, from another hospital on March 27, 1954, at 41 weeks' gestation with a diagnosis of acute lymphocytic meningitis, cause unknown.

Except for one attack of severe vertigo in February, 1954, the patient's prenatal course had been essentially uncomplicated up until the onset of her illness. Her last menstrual period was June 12, 1953. The total weight gain was 21¼ pounds. A routine chest x-ray on Sept. 14, 1953, was reported as being within normal limits. X-ray pelvimetry showed an ample gynecoid pelvis.

Her family history was noncontributory, but her past history disclosed pleurisy of a chronic nature 7 years before. This cleared after a year of nonspecific therapy.

The patient was first hospitalized on March 14, 1954, because of diplopia and severe headaches of three days' duration. Except for a moderate nuchal rigidity which persisted, neurological findings were essentially negative. A series of lumbar punctures showed elevated pressures (once to 420 mm.), elevated protein (100 to 150 mg. per cent), elevated lymphocyte counts (16 to 150), decreased sugar (31 to 36 mg. per cent), but an absence of pellicle formation. Direct smears and cultures of spinal fluid were negative for microorganisms. The colloidal gold curve was normal, the serologic test for syphilis negative. A complete blood count and blood chemistry determinations were within normal limits.

The patient ran a low fever and was treated with oral Terramycin. She became increasingly lethargic, finally semicomatose. In view of the clinical course, an acid-fast process or some other central nervous system lesion was suspected, and the patient was transferred to our care.

On admission to this hospital on March 27, 1954, the patient was semicomatose and restless. Physical examination revealed dilatation of the right pupil, left hemiparesis, complete of the left leg, partial of the left arm, a positive left Babinski sign, and nuchal rigidity. A 48-hour-old purified protein derivative tuberculin test was negative. Urinalysis showed 1 plus albuminuria. The uterus was enlarged to full term, and normal fetal

heart sounds were audible. Rectal examination disclosed a vertex presentation at minus 3 station, a partly effaced, closed cervix, and intact membranes. The rectal temperature was 99.6° F. and blood pressure 148/90. A lumbar puncture showed spinal fluid under marked pressure with a cell count of 133 lymphocytes, 3 polymorphonuclear leukocytes, and 20 red blood cells and a protein level of 156 mg. per cent.

Medical and neurosurgical consultants agreed that a space-occupying cerebral lesion must be excluded. Under Pentothal sodium anesthesia a right carotid arteriography was done and showed some thinning of the anterior cerebral artery as though it might be around a dilated ventricle. Ventriculography showed dilatation of the lateral and third ventricles without displacement of the ventricular system. Since at this time labor had commenced, it was deemed advisable to establish ventricular drainage with catheters through the burr holes for decompression until the termination of the labor, then proceed with further diagnostic studies.

During labor the patient emerged temporarily from her semicomatose state. After 11 hours and 30 minutes in the first stage and 35 minutes in the second stage, she was delivered under pudendal block anesthesia with low forceps of a full-term living male infant who weighed 7 pounds, 11 ounces. The placenta was carefully inspected and found to be grossly perfectly normal. A right mediolateral episiotomy was repaired and a Pitocin intravenous drip was used to control a mild degree of uterine atony. The patient remained semicomatose, and 12 hours post partum tachypnea necessitated a tracheotomy. Respirations improved temporarily, then suddenly ceased 13 hours post partum.

At autopsy the pertinent findings were limited to the brain and the right lung. The leptomeninges on the convex surface of the brain showed scattered small gray tubercle-like lesions particularly noticeable in the large median fissure. At the base of the brain there was a plastic exudate which covered the surface of the pons. Many small tubercles were seen in the region surrounding the chiasm and on the surfaces of both temporal lobes. There was a zone of infarction palpable in the Sylvian fissure on the right side. The aqueduct of Sylvius was small but was not grossly occluded. The roof of the fourth ventricle contained gray, cloudy adhesions. Sections of the brain for microscopic study showed an extensive tuberculous meningitis throughout all parts. The gross infarction was noted to be a zone of necrotic material. The inflammation was present in the cerebellar tissues as well as the cerebrum.

The thoracic cavity showed complete obliteration of the right pleural space by adhesions and about 100 c.c. of bloody fluid in the left pleural space. The lungs were markedly congested. A caseous mass measuring 1 cm. across was noted in the lateral basilar portion of the right upper lobe. Section through this part of the lungs revealed a large granuloma. This had a core of caseous material surrounded by a dense zone of fibrous tissue with several giant cells and epithelioid cells, also a great deal of calcium.

Acid-fast stains on brain tissue, on the necrotic material from the lung, and on lung tissue failed to reveal any organisms. A spinal fluid culture was found to be positive for *Mycobacterium tuberculosis* after seven weeks of incubation. There was no evidence of miliary disease in any of the body organs. The placenta, however, was not available for microscopic study.

The infant at this time is normal and healthy. Clinical and x-ray studies have been negative for evidence of acid-fast infection. Two purified protein derivative tuberculin tests were negative.

Summary

1. An additional case of tuberculous meningitis in pregnancy is reported.

2. The correct diagnosis was not made in time to institute specific tuberculocidal therapy.

3. Cerebral ventricular drainage established in the course of diagnostic studies eliminated possible objections to vaginal delivery.

4. The patient died 13 hours post partum, but the infant survived and was not affected by the tuberculous process.

I wish to express my sincere appreciation to Lieutenant J. T. Boswell (MC) USN, and Dr. M. G. Netsky for their pathological study of this case.

References

1. Schaefer, G., Douglas, R. G., and Dreishpoon, I. H.: Am. J. Obst. & Gynec. **67**: 605, 1954.
2. Lundström, P.: Act. obst. et gynec. scandinav. **27**: 84, 1947.
3. Kane, F. F.: Brit. M. J. **1**: 585, 1950.
4. Swift, P.: Brit. M. J. **2**: 787, 1950.
5. Silverman, E. G., and Feinblatt, T. M.: New York J. Med. **48**: 2280, 1948.
6. Rutberg, E.: Nord. med. **45**: 437, 1951.
7. Downs, W. J., and Clarke, T. R.: Canad. M. A. J. **66**: 475, 1952.
8. Rogers, W. N., Wilson, E., and Goodier, T. E. W.: J. Obst. & Gynaec. Brit. Emp. **57**: 795, 1950.
9. Faugère, G., and Fréour, P.: Rev. franç. gynéc. **45**: 72, 1950.
10. Goodwin, R. H., and Kenler, Maurice D.: New England J. Med. **246**: 15, 1952.
11. Bunn, P. A.: Am. J. M. Sc. **219**: 127, 1950.
12. Fitzpatrick, M. J.: Am. Rev. Tuberc. **69**: 370, 1954.
13. Beck, A. C.: Obstetrical Practice, Baltimore, 1939, Williams & Wilkins Company, p. 591.
14. Rand, C. W., and Andler, M.: Arch. Neurol. & Psychiat. **63**: 1, 1950.

RENAL-CELL CARCINOMA COMPLICATED BY PREGNANCY*

A Case Report

HARRY K. WADDINGTON, M.D., CHICAGO, ILL.

(From the Department of Obstetrics and Gynecology, University of Illinois, College of Medicine and the Department of Obstetrics, South Shore Hospital)

MALIGNANT epithelial tumors of the kidney are a relatively uncommon lesion, and their appearance in young women is rare. Willis[1] found a 2½ per cent incidence of these tumors in 1,060 autopsies with 50 per cent appearing in the fifth and sixth decades of life and he stated that they are rare under the age of 30. They are more frequent in males with sex ratios varying from 3:2 to 5:1 in reported series. The classical symptom is hematuria; less common is the presence of a mass or pain.

Many synonyms have been given this type of carcinoma since the first described case: Grawitz tumor, hypernephroma, clear-celled carcinoma, solid-celled carcinoma, etc. Consensus today, however, favors the term renal-ceil carcinoma.

Because of the markedly decreased incidence of this uncommon tumor in women in the childbearing age, its association with pregnancy is a rare occurrence. A review of the literature discloses only 7 authenticated cases of renal-cell carcinoma complicated by pregnancy (Table I). The following additional case is reported.

Case Report

E. P., a 27-year-old gravida i, para 0, was admitted to the obstetrical service of South Shore Hospital at 10:15 P.M. on March 15, 1953, complaining of cramping lower abdominal pain and pronounced vaginal bleeding of about one hour's duration. Her last menstrual period was Aug. 17, 1952, and her estimated date of confinement May 24, 1953. The prenatal course had been uneventful and all findings had been within normal limits. A chest x-ray taken Nov. 7, 1952, was reported as normal.

Examination one hour after admission showed an apprehensive, acutely ill woman lying in bed. Temperature, pulse, and respirations were normal; the blood pressure was 140/90. Physical examination showed the head, neck, heart, and lungs to be normal. The abdomen was distended by a pregnant uterus of approximately 28 to 30 weeks' gestation which was contracting every five minutes. The fetus was in left sacrotransverse position, floating, the fetal heart tones 160. There was a large blood stain on the sheet beneath the patient and several large clots up to 4 to 5 cm. in diameter were seen escaping from the introitus. The red blood count was 3.50 million, white blood count 16.1 thousand, and hemoglobin 9.5 Gm. per 100 ml.

The immediate impression was abruptio placentae. Blood was cross-matched and the patient was prepared for sterile vaginal examination. This showed the cervix to be long and closed, and there was no blood in the vagina. Catheterization of the urinary bladder revealed almost pure blood with several large clots. The patient was then put to bed and sedation given. Urinary bleeding continued but in lessened amounts.

*Presented at a meeting of the Chicago Gynecological Society, April 15, 1955.

TABLE I

AUTHOR	AGE	GRAVIDITY	TREATMENT	PATHOLOGICAL DIAGNOSIS	OUTCOME OF PREGNANCY	MATERNAL RESULT
1. Kneise[4]	20	?	Nephrectomy at 9 months' gestation	Hypernephroma	Spontaneous delivery of living child 3 days post nephrectomy	When last seen patient steadily losing weight
2. Kulitzy[4]	35	iv	Nephrectomy at 5 months' gestation	Hypernephroma	Not stated	Living and well 5 years
3. Henriksen and Spense[2]	40	v	Irradiation at 3 months' gestation, nephrectomy at 6 months' gestation	Hypernephroma	Cesarean section, 1,540 gram living infant	Living and well 9 months
4. Hoffman[3]	31	i	Nephrectomy at 16 weeks' gestation	Hypernephroma	Cesarean section, 2,130 gram living infant	Living and well 21 months post section
5. Vitt and Melick[4]	21	?	Nephrectomy 4½ months postpartum	Papillary adenocarcinoma	Low forceps delivery of 6 pound, 4 ounce infant	Living and well 2 years
6. Lash[5, 6]	30	ii	Nephrectomy 35 days postpartum	Clear-cell adenocarcinoma	Cesarean section, living infant	Living and well
7. Jones and Price[7]	30	?	Nephrectomy at 3 months' gestation, followed by x-ray	Granular-cell adenocarcinoma	Aborted 2 months postoperatively	Living and well 9 months
8. Waddington	27	i	Nephrectomy 6 days postpartum	Clear-cell carcinoma	Cesarean section, 4 pound, 14¼ ounce living infant	Living and well 34 months

Urological consultation was requested for investigation of the gross hematuria. The urologist advised conservative management for a short period to see if bleeding would stop, with cystoscopy to be done at a later date. Gantrisin and vitamin K were given along with Demerol as needed for pain. A transfusion of 500 c.c. of whole blood was also given.

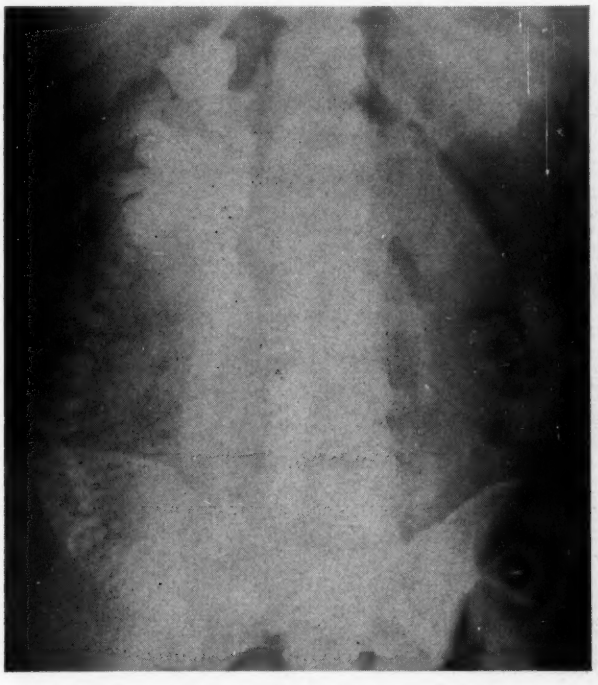


Fig. 1.—Intravenous pyelogram showing dilated right kidney and ureter, and nonfunctioning left kidney.

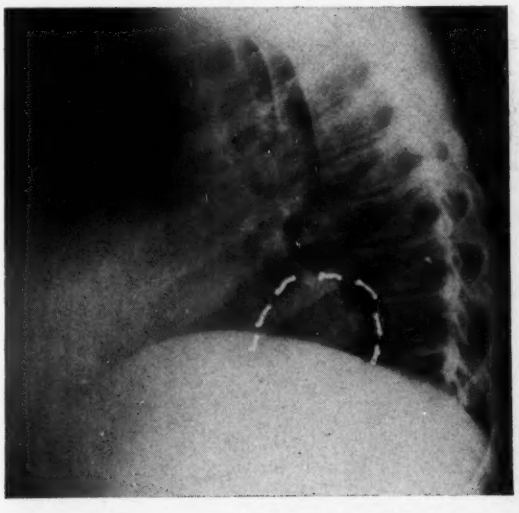


Fig. 2.—Chest x-ray showing "cannon-ball" metastasis in right base posteriorly.

On March 23, 1953, cystoscopy and retrograde pyelography were done. The bladder was filled with clots, but on their removal blood was seen coming from the left ureter. Retrograde pyelograms showed the right ureter and kidney to be normal with the typical dilatation found in pregnancy. The left ureter was filled with clots and the left pelvis and calyces could not be visualized.

Hematuria continued and transfusions were necessary every two to three days to maintain the red cell count at about 3.5 million. Intravenous pyelography April 1, 1953, was reported: "Enlargement of and non-functioning left kidney, and moderate right hydro-ureter and hydronephrosis" (Fig. 1). The Mantoux test was negative.

Fig. 3.—Surgical specimen with tumor in upper pole.

Fig. 4.—Photomicrograph of renal-cell carcinoma.

Chest x-ray was repeated on April 11, 1953, and showed a rounded, sharply defined shadow of soft-tissue density projected over the right base medially, which appeared to be in the medial basal segment of the right lower lobe and which measured 6 cm. in diameter

(Fig. 2). In view of the large, so-called "cannon-ball" metastasis and the gross hematuria, a clinical diagnosis of renal-cell carcinoma was made and renal exploration advised. This was refused by the patient.

Her condition declined slowly and on April 17, 1953, the nonprotein nitrogen, which had previously been within normal limits, was 48 mg. per cent. As the patient's right kidney was now failing, it was decided to terminate the pregnancy in spite of the small size of the infant.

A living premature female infant weighing 4 pounds, 14 ounces, and in good condition, was delivered by low cervical cesarean section under spinal anesthesia on April 18, 1953. The left kidney was found to be hard and twice normal size by palpation.

The immediate postoperative condition was good, although hematuria persisted. On April 24, 1953, the sixth postoperative day, massive hematuria occurred and the patient rapidly went into shock. The pulse was shallow and too rapid to count, while blood pressure dropped to 30/0. Following a transfusion of 3,500 c.c. of whole blood, emergency left nephrectomy was done. The postoperative period was relatively uneventful.

The pathologist's report was as follows: *Gross:* The kidney measured 16 by 7.5 by 6 cm. At one pole the kidney tissue was replaced by a tumor 5 by 6 by 5 cm. The tumor was markedly hemorrhagic and soft. Some of the tumor tissues were gray yellow. The pelvis and calyces were markedly dilated. One calyx had a diameter of 3 cm. The ureter was dilated and had a circumference of 1.5 cm. and was 6 cm. long. Adjacent to the tumor mass was a cystic structure 5 cm. in diameter. This was filled with blood clot. The parenchymal tissue was gray red and smooth (Fig. 3). *Microscopic:* Tissue from the region of the tumor was made up of cells which had rather small nuclei and pale foamy or vacuolated cytoplasm. There were large regions of necrosis also. Mitotic figures were not observed (Fig. 4). *Diagnosis:* Kidney, clear-cell carcinoma with hemorrhage and hydronephrosis.

Skull and long bone x-rays taken during the postoperative period showed no other metastases. The patient was discharged May 5, 1953, the forty-seventh hospital day. She had received twenty-four units of blood.

As she apparently had a solitary metastasis, she was admitted to Research and Educational Hospitals June 10, 1953, for possible pneumonectomy. Surgical exploration June 15, 1953, revealed a defect in the right diaphragm which would admit three fingers, through which liver was herniated, and which gave rise to the shadow of the "cannon-ball metastasis" seen on x-ray.

Subsequent follow-up examinations, the last on Feb. 3, 1956, showed the patient to be living and well with no evidence of recurrence of the carcinoma. She reported the infant to be normal. There have been no further pregnancies.

Summary

1. A case of renal-cell carcinoma complicated by pregnancy is presented.
2. This is the eighth such case reported.

I am indebted to Drs. Armando Abadin and Herbert S. Doroshow for their assistance in caring for this patient.

References

1. Willis, R. A.: Pathology of Tumours, St. Louis, 1948, The C. V. Mosby Company.
2. Henriksen, E., and Spense, J. M.: J. A. M. A. **108**: 22, 1937.
3. Hoffman, G. L.: AM. J. OBST. & GYNEC. **38**: 514, 1939.
4. Vitt, A. E., and Melick, W. F.: J. Urol. **48**: 601, 1942.
5. Lash, A. F.: AM. J. OBST. & GYNEC. **50**: 221, 1945.
6. Lash, A. F.: Personal communication.
7. Jones, R. F., and Price, K. A.: J. Nat. M. A. **41**: 143, 1949.

A CASE OF HYPOFIBRINOGENEMIA FOLLOWING VAGINAL SURGERY

With the Subsequent Development of Homologous Serum Jaundice

WILLIAM J. SWEENEY, M.D., NEW YORK, N. Y.

(From the Department of Obstetrics and Gynecology, Cornell University Medical College, and The Woman's Clinic of The New York Hospital)

IT HAS been known for many years that clots formed by normal whole blood or recalcified citrated or oxalated blood will remain intact in their own serum for days or even weeks if bacterial growth is prevented. Under certain circumstances this stability is lost so that either no clots are formed or, if coagulation does occur, the clot breaks up and disappears.[1]

By far the majority of the recent papers have dealt with hypofibrinogenemia in pregnancies complicated by severe abruptio placentae, amniotic fluid emboli, and fetal death in utero. More and more publications are appearing, however, in which hypofibrinogenemia has developed during surgical operations.[2-15] The following report presents a case of hypofibrinogenemia which developed during a Manchester vaginal plastic operation on a patient who subsequently suffered from homologous serum jaundice.

The patient, M. D., a 39-year-old para ii, gravida vii, Irish-born woman was admitted to the New York Lying-In Hospital for the second time on Oct. 27, 1953, with a history of urinary incontinence and a vaginal discharge. Her first admission had been on Oct. 13, 1953, with the same complaints, but she had been discharged because of the onset of her menstrual period on Oct. 12, 1953.

For eleven years the patient had noted frequency, dysuria, and increasing incontinence. For three years prior to admission she had noted vaginal discharge and pruritus.

During the patient's early life in Ireland her diet was extremely poor and when she moved to New York City at the age of 15 she weighed 92 pounds. As a child she had frequent episodes of severe epistaxis, but denied any other abnormal bleeding tendencies. After moving to this country she secured work as a domestic, but recalls having to give up several positions because of the recurrence of the severe nosebleeds.

She was married in 1934. In 1934 she had a spontaneous abortion. In 1938 she had an operative delivery at term followed by a postpartum hemorrhage treated with ice packs, but in 1942 she had an uneventful pregnancy and delivery. In 1945 and 1946 she had spontaneous abortions which were not complicated by excessive bleeding. In 1947, however, she had a spontaneous abortion followed by a massive hemorrhage which was again treated with ice packs. Four months prior to her first admission to The Woman's Clinic of The New York Hospital she had another spontaneous abortion followed by a massive hemorrhage.

In 1935 she had a uterine suspension and an uneventful postoperative course. In 1941 she was in an automobile accident and suffered minor bruises and abrasions, but exhibited no bleeding tendency. In 1949 she had an episode of massive hematemesis and was hospitalized at another hospital and, while there, had a severe epistaxis which required packing. In 1953, she had a ligation of the saphenous vein with no evidence of excessive bleeding.

The patient's menstrual periods had always been regular since the age of 14 and had recurred every twenty-eight days with no abnormal bleeding. Her previous menstrual period was Sept. 10, 1953, and her last menstrual period had been Oct. 12, 1953.

The pelvic examination before operation revealed a parous outlet with a large cystocele, urethrocele, and rectocele. The cervix was hypertrophied with a large central erosion. The blood pressure was 140/80. Laboratory examinations included negative x-rays of the lumbosacral spines with no evidence of an occult spina bifida; negative gall bladder series; and a negative cystoscopy except for marked telangiectatic areas of the bladder mucosa. Urethroscopy revealed a gaping urethrovesical junction with no change of shape on straining or holding. A cervical biopsy was reported to show chronic cystic cervicitis.

On Oct. 28, 1953, at 10:10 A.M., the patient was given atropine, 0.4 mg. and morphine sulfate, 8 mg. The dilatation and curettage and anterior repair were begun under cyclopropane anesthesia at 12:25 P.M. and marked bleeding was noted almost immediately. The blood pressure at this time was 120/80. At 12:50 P.M. the anterior repair and the amputation of the cervix were completed and the first 500 c.c. of whole blood had been given. The blood pressure at this time was recorded as 110/70. At 1:20 P.M. the second unit of blood was given and at this time the reconstruction of the cervix and the posterior colporrhapy had been completed. There continued to be generalized bleeding from all areas of the operative site and the anterior vaginal wall was reopened, but no active bleeders could be found. At this point the blood pressure had dropped to 90/60 and blood was obtained for a fibrinogen determination.

The anterior vaginal wall was resutured and this time Fothergill-type sutures and tight vaginal packing were employed in an unsuccessful effort to establish hemostasis. Administration of a third unit of blood with 8 mg. of vitamin K added was begun and at this point the fibrinogen level by the rapid method of Bonsnes[16] was reported and revealed hypofibrinogenemia. Three grams of fibrinogen was administered and the vagina was repacked. Within minutes after the fibrinogen had been given the bleeding ceased and the blood pressure rose to the preoperative level of 120/80. At this time the quantitative test for fibrinogen had been completed and was reported as 20 mg. per cent.

The patient was observed in the operating suite for the next three hours. She was then returned to her room fully conscious with a blood pressure which had been maintained at 120/80 and with no further evidence of bleeding.

On October 29, half of the vaginal packing was removed with no recurrence of bleeding and the following day the remainder of the packing was removed. There was no evidence of further bleeding until Nov. 3, 1953, when the patient had an episode of vaginal bleeding of undetermined origin. This ceased spontaneously after a period of thirty minutes. The fibrinogen level at this time was 440 mg. per cent. The patient had an uneventful subsequent hospital stay and was discharged on Nov. 13, 1953.

Subsequent Course.—On Dec. 18, 1953, seven weeks after the operation, the patient was seen in the follow-up clinic and at this time had no complaints. On Jan. 20, 1954, however, she began to notice an epigastric fullness followed by nausea and vomiting and the development of clay-colored stools and dark urine. On February 8 she noted a generalized pruritus and the development of jaundice. She was admitted to the Surgical Service of The New York Hospital on February 12 and transferred to the Medical Service on February 18 with a diagnosis of homologous serum jaundice.

On Feb. 23, 1954, at 8:30 A.M., she began to have active bleeding from the right nostril which was treated with cocaine, epinephrine, and packing. At 3:15 P.M. she again began to have active bleeding from the right nostril which was again packed. A rapid fibrinogen determination was done and this was found to be within normal limits. Despite this finding, 3 Gm. of fibrinogen was given and the bleeding stopped with no further epistaxis. The quantitative fibrinogen level in the blood sample which had been used for the qualitative test was reported as 394 mg. per cent. No examination for the presence of a fibrinolysin was carried out.

The patient had no further bleeding during the remainder of her hospital stay. On March 24, 1954, she had an upper right bicuspid extraction with no hemorrhagic difficulty and subsequently, as the clinical and laboratory signs of hepatic function returned to normal, she was discharged on April 6, 1954.

On May 13, 1954, the patient was seen in the gynecological follow-up clinic and vaginal examination showed a good postoperative result. On July 28, 1954, she was seen in the medicine follow-up clinic, where examination showed the liver edge at the costal margin, but no residual signs of the homologous serum jaundice. Bromsulphalein test was done and showed a 3.9 per cent retention.

Comment

The actual cause or causes of the development of the hypofibrinogenemia in the presented case cannot be determined. It is possible that enough tissue thromboplastin from the raw denuded operative area could have been liberated to cause intravascular fibrin deposition with subsequent depletion of the fibrinogen level to 20 mg. per cent, or there may have been an increased fibrinolytic activity as a result of an unbalanced coagulation-anticoagulation system. There must, however, have been a still unknown factor which caused this patient to develop this hemorrhagic tendency with the same surface area of operation, the same technique, and the same amount of tissue damage as the patient who preceded her and the patient who followed her on the operative schedule.

The subsequent development of homologous serum jaundice is difficult to blame on the fibrinogen because she also had received whole blood transfusions. When the decision is made to employ fibrinogen in any given case, however, one must seriously consider the possibility of subsequent development of homologous serum jaundice. The incidence of this distressing complication is much higher after the administration of fibrinogen than after the use of carefully prepared compatible whole blood. The fear of homologous serum jaundice should not prevent the use of fibrinogen, but its use must be reserved for the *proved* case of hypo- or afibrinogenemia.

Summary

A case is presented of hypofibrinogenemia which developed during a Manchester vaginal plastic operation in a patient who subsequently suffered from homologous serum jaundice.

References

1. MacFarlane, R. G., and Pilling, J.: Lancet 2: 562, 1946.
2. Foster, D. P., and Whipple, G. H.: Am. J. Physiol. 58: 407, 1922.
3. Coon, W. W., and Hodgson, P. E.: Surg., Gynec. & Obst. 95: 717, 1952.
4. Steiger, W. A., Zeafonetis, C. J., Wilson, D., and Buchan, C. T.: Obst. & Gynec. 2: 99, 1953.
5. Tagnon, H. J., Levenson, S. M., Davidson, C. A., and Taylor, F. H.: Am. J. Med. Sc. 211: 88, 1946.
6. Hidalgo, J., Fowell, A. H., and Ralls, R. J.: Surg., Gynec. & Obst. 95: 661, 1952.
7. Mathey, J. J., Doumet, P. H., Soulier, J. P., Le Ballough, A. G., and Fayet, H.: Mém. Acad. chir. 76: 977, 1950.
8. Chanutin, A., Hortenstine, J. G., Cole, W. J., and Ludwig, S.: J. Biol. Chem. 123: 247, 1938.
9. MacFarlane, R. C.: Lancet 1: 10, 1937.
10. Scott, E. V. Z., Matthews, W. F., Butterworth, C. E., and Frommeyer, W. B.: Surg., Gynec. & Obst. 99: 679, 1954.
11. MacFarlane, R. G., and Biggs, R.: Lancet 2: 862, 1946.
12. Ratnoff, O. D.: J. Clin. Invest. 5: 521 1952.
13. Imperati, L.: Riforma med. 53: 1694, 1937.
14. Tagnon, H. J., Whitmore, W. F., Jr., Shulman, P., and Kravitz, S. C.: Cancer 6: 63, 1953.
15. Tagnon, H. J.: Cancer 5: 9, 1952.
16. Bonsnes, R. W., and Sweeney, W. J.: Am. J. Obst. & Gynec. 70: 334, 1955.

ADENOCARCINOMA OF THE APPENDIX WITH KRUKENBERG TUMOR OF THE OVARIES

RICHARD M. NUNNALLY, M.D., AND P. O'B. MONTGOMERY, M.D., DALLAS, TEXAS

(From the Department of Pathology, Southwestern Medical School of the University of Texas)

IN 1896 Krukenberg described a peculiar malignant tumor of the ovaries which he designated "fibrosarcoma mucocellulare carcinomatodes." Ewing[1] describes Krukenberg's first case as presenting large bilateral ovarian masses of considerable dimensions, maintaining the form of the ovaries, and ultimately causing the death of the patient associated with extension and recurrence. Subsequent reports have shown that these are usually metastatic tumors, arising from primary adenocarcinomas of the abdominal viscera. The great majority originate in the stomach or large intestines.[2, 3] In a review of the literature we have been able to find only two cases of primary adenocarcinoma of the appendix associated with isolated ovarian metastases, and in each of these instances the appendix contained a mucocele.[4, 5] It is the purpose of this paper to present a case of primary adenocarcinoma of the appendix unassociated with mucocele which gave rise to Krukenberg tumors of the ovaries.

Case Report

The patient was a 55-year-old gravida iii, para iii, Negro woman, whose chief complaint was pain in the lower abdomen of three months' duration.

On physical examination, the positive findings were confined to the abdomen and pelvis. Multiple large, firm masses were palpated in the lower abdomen, several of which were believed to be attached to the uterus.

At operation the uterus was found to contain several large nodules scattered beneath the serosal surface. The right ovary consisted of a large, round, solid mass, mottled red and yellow in color, and covered by a thick glistening capsule. This mass was approximately 11 cm. in diameter and was found low in the pelvic cavity, posterior to the uterus and close to the midline. There was a similar mass, estimated to be 7 cm. in diameter, occupying the usual position of the left ovary. The appendix was found lying over the rim of the pelvis and was attached to the right ovarian mass by a few fibrinous adhesions which were easily detached. The distal two-thirds of the appendix was thickened and firm in consistency. The outer surface of the appendix was smooth and glistening and grayish white in color. The peritoneum was smooth and no remarkable lymph nodes were palpable. Only the lower portion of the liver could be felt and this was normal. A total hysterectomy, bilateral salpingo-oophorectomy and appendectomy were performed.

Pathology Report.—The specimen consisted of a uterus measuring 10 cm. in length, the surface of which was covered by numerous firm nodules, ranging from 0.5 to 3.5 cm. in diameter. Received separately were two large, solid tumor masses measuring 11 and 7 cm. in diameter. These were surrounded by a glistening white capsule measuring 1 mm. in thickness. The cut surfaces of these tumors were smooth, yellowish white, and homogeneous in appearance with several small, irregular cystic spaces 2 to 3 mm. in diameter,

scattered within the substance of the tumor. A small amount of gray mucoid material was found within the cystic spaces. The appendix measured 8 cm. in length and the uniform diameter of the distal two-thirds was 9 mm. The proximal third of the appendix measured 6 mm. in diameter. The distal two-thirds was grayish white in color, firm in consistency, and moderately hyperemic. The proximal one-third was pink and of the usual consistency. On cut section, the lumen of the distal third was completely obliterated by dense white tissue arranged in a whorled concentric appearance.

Microscopic examination of the appendix showed the lesion to be adenocarcinoma arising in a background of fibrous obliteration of the appendix. The carcinoma was arising in the center of the appendix and spreading in an even centrifugal dispersion to involve the subserosa. The carcinoma consisted of small nests and cords of neoplastic cells which occasionally arranged themselves into small glandlike structures with lumina.

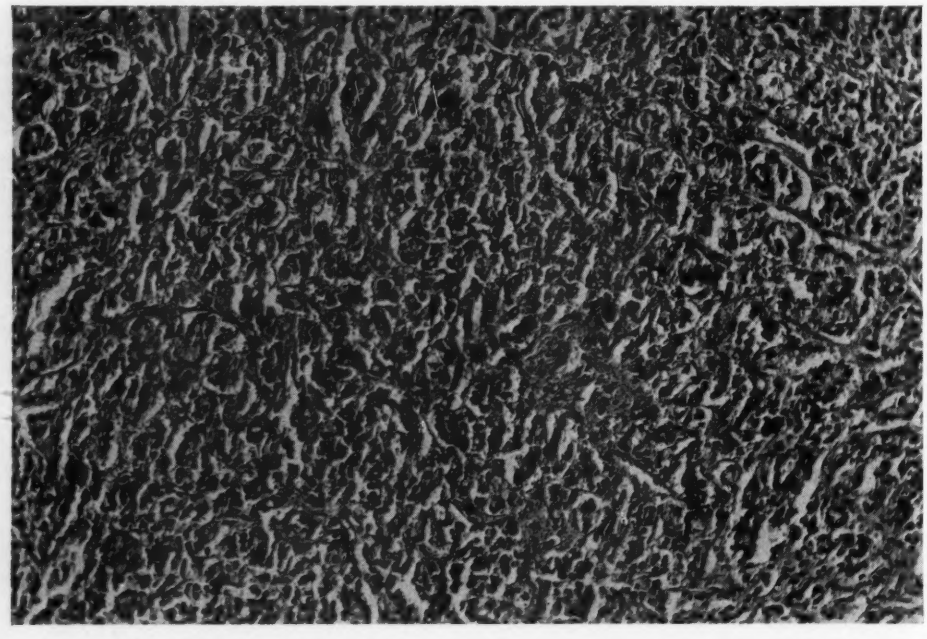


Fig. 1.—Krukenberg ovarian carcinoma, primary site appendix.

Some of the tumor cells had mucoid material in their cytoplasm. This material pushed the nucleus to one side, giving a signet-ring effect. Best mucicarmine stain showed the material to take a positive stain. Silver stains failed to demonstrate any silver-positive material within the tumor cells. Microscopic examination of the sections of the ovary revealed an identical tumor invading and replacing the ovarian stroma (Fig. 1). Here the tumor was arranged in small nests or cords or strands, or as isolated little glands, while in other areas it was diffusely infiltrating and separating the ovarian stroma as single cells or columns of single cells. Sections taken from the nodular tumors within the uterine wall revealed well-differentiated leiomyomas characterized by dense whorls of fibromuscular tissue.

Course and Treatment.—The patient was transferred to the Surgery Service to be prepared for a right colectomy. Over a period of several weeks it was difficult to maintain the patient's hemoglobin at an adequate level and several blood transfusions were required. Four weeks after the first operation, the abdomen was re-explored through a transverse abdominal incision. Many small, firm, white nodules, 4 to 5 mm. in diameter, were found scattered over the pelvic and peritoneal surfaces. Large retroperitoneal aortic glands were palpable and a

nodule approximately 1.5 cm. in diameter was palpable under the surface of the liver. The tumor was considered inoperable and the abdomen was closed. The patient's postoperative course was uneventful and she was discharged to be followed in the outpatient clinic.

Comment

It is generally accepted that malignant lesions of the appendix fall into three histological groups: malignant mucoceles, argentaffin tumors (carcinoids), and colonic or true adenocarcinomas.[6, 7] This classification was first suggested by Uihlein and McDonald[8] in 1943. A review of 36 cases of primary appendicular adenocarcinoma, as reported or compiled by Young and Wyman,[9] Uihlein and McDonald,[8] Hilsabeck,[7] Lesnick and Miller,[5] Hughes,[10] Lawton and Ehrlich,[6] and McCampbell and Dickinson[11] reveals certain features of interest. The usual route of extension from appendicular carcinoma is by invasion of the cecum and through lymphatic channels to regional lymph nodes and the liver.[5, 7, 12] Several cases which eventuated in generalized abdominal carcinomatosis have been described.[5] Metastases to the ovaries are infrequent. It has been suggested by some that the case reported by Whipham[13] in 1901 of spheroidal-cell carcinoma of the appendix which showed widespread pelvic seeding and a large left-sided ovarian mass was an adenocarcinoma of the appendix. The microscopic reproductions of this tumor of the appendix, included in the original article, show masses of spheroidal-shaped cells without gland formation and separated by thin bands of loose fibrous connective tissue, a picture typical of carcinoid tumors. In 1928 Horning[4] described a case of carcinoid of the appendix with involvement of both ovaries and stated that spread may occur by implantation or from retrograde lymphatic drainage. Willis[14] mentions a case of carcinoid of the appendix reported by Barth in 1929 with metastases to the right ovary. A silver stain of the tissue was not described. The patient was reported well several years after surgical removal of both tumors. Most authorities agree that true Krukenberg tumors are universally fatal, and that treatment is entirely surgical since radiation has proved to be of little value.[1, 10]

The two verified cases of primary adenocarcinoma of the appendix with metastatic involvement of the ovaries have been reported by Waugh and Findley[4] in 1937 and Lesnick and Miller[5] in 1949. The primary lesion in the case of Waugh and Findley was a mucocele of the appendix with adenocarcinomatous transformation of the mucosa. The appendix had ruptured and carcinomatous implants were scattered diffusely over the ovaries and pelvic peritoneum. Lesnick and Miller described a case of primary adenocarcinoma of the base of the appendix in conjunction with a mucocele distal to the constricting carcinoma. The patient later developed bilateral ovarian tumors which grossly and microscopically were Krukenberg in type. Our case appears to be the only reported occurrence of primary adenocarcinoma of the appendix with bilateral ovarian metastases, not associated with either a mucocele or carcinoid tumor.

Summary

A case of primary adenocarcinoma of the appendix with Krukenberg tumors of the ovary is described.

References

1. Ewing, J.: Neoplastic Diseases, ed. 4, Philadelphia, 1940, W. B. Saunders Company, p. 662.
2. Ackerman, L. V.: Surgical Pathology, St. Louis, 1953, The C. V. Mosby Company, p. 570.
3. Norris, J. C.: South. M. J. **47**: 116, 1954.
4. Waugh, T. R., and Findley, D.: Am. J. Surg. **37**: 518, 1937.
5. Lesnick, G., and Miller, D.: Cancer **2**: 18, 1949.
6. Lawton, S. E., and Ehrlich, M. D.: J. A. M. A. **150**: 189, 1952.
7. Hilsabeck, J. R.: Proc. Staff Meet., Mayo Clin. **28**: 11, 1953.
8. Uihlein, A., and McDonald, J. R.: Surg., Gynec. & Obst. **76**: 711, 1943.
9. Young, E. L., and Wyman, S.: New England J. Med. **227**: 703, 1942.
10. Hughes, J. H.: Brit. J. Surg. **39**: 282, 1951.
11. McCampbell, B. R., and Dickinson, E. H.: U. S. Armed Forces M. J. **3**: 125, 1952.
12. Woolner, F. B.: Proc. Staff Meet., Mayo Clin. **28**: 17, 1953.
13. Whipham, T. R. C.: Lancet **1**: 319, 1901.
14. Willis, R. A.: The Spread of Tumors in the Human Body, St. Louis, 1952, The C. V. Mosby Company, p. 96.

AN INSTRUMENT TO AID IN VAGINAL PLASTIC SURGERY

JOHN C. BODLE, M.D., SALT LAKE CITY, UTAH

(From the Department of Gynecology, Holy Cross Hospital)

VAGINAL plastic surgery has always been a back-breaking task for the assistants. Doctors operating in hospitals with insufficient house staffs, or none at all, find vaginal surgery difficult and slow with but one assistant. One answer to this problem is a mechanical retractor. Such an instrument has been devised and found to be of great help. It has been used by me and several others at our hospital for the past three months.

Fig. 1.—"Robot" in use (front view).

The "Robot"* is made from a rod of stainless steel shaped in such a fashion as to fit over the perineum and fasten to the standard bar on the sides of the operating table. From this arc are suspended the Allis forceps which are attached on the vaginal mucosal flaps. The vehicle of attachment is that of a standard 2 inch rubber band (Fig. 1). The instrument is attached to the table after the patient has been draped in the usual manner for vaginal surgery. Both arc and rubber bands can be autoclaved without difficulty.

The advantages of this instrument are multiple. The need for manual retraction on the vaginal flaps is obviated. There is equal tension on the vaginal mucosa at all times. Hands are kept out of the operative field and left free to sponge, tie sutures, and retract in special needed places. Above all, it makes it possible for the operator and one assistant easily and quickly to perform vaginal plastic surgery which usually requires two or more assistants.

The rubber bands apply tension equally. They can be slipped up or down the arc and are fastened by the simple motion of wrap around and pull through. The finger loops of the holding forceps are slipped through the rubber band loop. They can be freed readily by reversing the movement.

Conclusion

A simple and effective instrument is presented to be used for retraction of vaginal flaps in vaginal surgery.

*The instrument was constructed by the V. H. Bodle Specialty Supply, 5615 No. Robinhood Ave., Temple City, Calif.

MYOMA OF THE VAGINA

Case Report

DAVID M. FARELL, M.D., AND JEROME ABRAMS, M.D., PHILADELPHIA, PA.

(From the Department of Obstetrics and Gynecology, Jefferson Medical College Hospital)

THE earliest reference to a myoma occurring in the vagina seems to be that of Denys de Leyden[1] who described a "fibrous tumor" of the vagina in 1733. Although during the succeeding years there were several reports of varying degrees of thoroughness, it was not until 1882 that an authoritative review of 53 cases of fibromas, myomas, and fibromyomas was published.[2] In 1934, Scheffey and Farell[3] reviewed the literature, collecting 162 cases, and added one case. The next review of the literature was that of Bennett and Ehrlich[4] in 1941, when they estimated that approximately 200 cases had been reported. Since this most recent survey, there have been four[5, 6, 7, 8] separate cases reported in the United States and approximately fourteen cases reported in the foreign literature.

Fig. 1.—Photomicrograph showing myoma of vagina.

In the past, the terms fibromyoma, myofibroma, fibroma, and fibroid were used to describe this lesion; however, in view of the generally accepted opinion that it is of muscle-tissue origin, myoma or more exactly leiomyoma is considered the correct term.[9]

Mrs. C. S., a 45-year-old white woman, was admitted to the Jefferson Medical College Hospital on Jan. 5, 1955, for the surgical management of a "lump in the vagina." The lump was first discovered upon routine pelvic examination by the patient's family physician approximately three months prior to hospital admission. The patient experienced no

specific complaints referable to the vaginal lesion. On Jan. 6, 1955, under Pentothal sodium anesthesia, pelvic examination showed a moderately firm, freely movable mass, approximately 2 cm. in diameter, located in the left anterior wall of the vagina, and a small mobile uterus anterior in position; the patient underwent dilation and curettage, cervical conization, and enucleation of the vaginal lesion. The defect in the vaginal wall was readily repaired with chromic catgut sutures. The postoperative course was uneventful and the patient was discharged on Jan. 10, 1955.

The pathologic diagnoses were proliferative endometrium, chronic cystic cervicitis, and leiomyoma with hyaline change.

The histologic report of the nodule of the vaginal wall (Fig. 1) was as follows: "The tumor is encapsulated and composed of cell-poor muscle and fibrous cells. Localized areas of hyaline changes are noted throughout the tumor. There is no evidence of malignancy."

Comment

Myomas of the vagina are usually single and only occasionally multiple; more than half occur in the anterior wall. The majority of these tumors measure approximately 3 to 4 cm. in diameter; the largest vaginal myoma measured 20 cm. in diameter.[10] Myomas of the vagina occur most frequently between the ages of 38 and 48, and predominantly in white women; this latter fact is particularly interesting in view of the fact that uterine myomas occur three times more frequently in Negro women. There has been no correlation noted between the occurrence of vaginal myomas and the occurrence of uterine myomas in the same patient.

Myomas of the vagina are usually moderately firm, but since they may undergo the same degenerative changes as those of the uterus, i.e., hyalinization, calcification, liquefaction, necrosis, cystic degeneration, etc., they may vary in consistency from firm to soft. It is this variation in consistency that is largely responsible for the relative difficulty in preoperative diagnosis. Malignant tumors, epithelial cysts, endometriosis, cystocele, and prolapse must be considered in the differential diagnosis. Bennett and Ehrlich[4] collected nine cases of vaginal myoma out of 50,000 case specimens which included 19 cases of primary vaginal carcinoma and 100 cases of epithelial cysts. The practical approach to any vaginal mass would entail immediate excision.

Summary

Approximately 220 cases of myoma of the vagina have been reported. A case of a 45-year-old white woman with a myoma of the vagina, not associated with uterine myoma, has been reported.

References

1. Tourneux, J. P.: Progrès méd. **41**: 1569, 1934.
2. Kleinwaechter, L.: Ztschr. f. Heilk. **3**: 335, 1882.
3. Scheffey, L. C., and Farell, D. M.: Am. J. Obst. & Gynec. **29**: 731, 1935.
4. Bennett, H. G., and Ehrlich, M. M.: Am. J. Obst. & Gynec. **42**: 314, 1941.
5. Scott, G. D., and Scott, I. H.: Am. J. Surg. **54**: 391, 1941.
6. Shanahan, T. H.: Am. J. Surg. **56**: 513, 1942.
7. Schulte, W. G., and Middleton, R. P.: Rocky Mountain M. J. **39**: 762, 1942.
8. Strickland, C. G.: Pennsylvania M. J. **47**: 489, 1944.
9. Novak, E.: Gynecologic and Obstetric Pathology, ed. 3, Philadelphia, 1952, W. B. Saunders Company.
10. Herbut, P. A.: Gynecological and Obstetrical Pathology, Philadelphia, 1953, Lea & Febiger.

Department of Reviews and Abstracts

EDITED BY LOUIS M. HELLMAN, M.D., BROOKLYN, N. Y.

Selected Abstracts*

Medical Journal of Australia

Vol. 1, April 30, 1955.

*White, V. T.: The Significance and the Management of Meconium in the Liquor Amnii During Labor, p. 641.

White: Significance and Management of Meconium in Liquor Amnii During Labor, p. 641.

Meconium-stained amniotic fluid has long been accepted as evidence of fetal distress. Since this may be the deciding factor in the decision to interrupt labor and to deliver an already compromised fetus by cesarean section (not in itself a *guarantee* of the infant's survival), the author has attempted to evaluate the significance of the sign.

Two hundred and seventeen (5 per cent) of 4,350 consecutive deliveries at the Marston Green Maternity Hospital demonstrated staining of the amniotic fluid. In 72 instances the fetus required resuscitation and this was the criterion of fetal distress.

Changes in the fetal heart tone were correlated with the finding of meconium-stained fluid and a less satisfactory prognosis could be expected if slowing of the heart was observed. The cause and the significance of both fetal bradycardia and meconium staining are discussed. Management depends upon whether there is meconium staining alone, meconium plus anoxia, or meconium and slowing of the fetal heartbeat.

ARTHUR PERELL, M.D.

Münchener Medizinische Wochenschrift

Vol. 97, No. 6, February 11, 1955.

Nachtscheim, H.: Frequency and Distribution of Pathological Genes in Human Population, p. 157.

Ehrengut, W.: On the Chromosomal Sex of Patients With Agenesis of the Gonads, p. 162.

Vol. 97, No. 7, February 18, 1955.

Bernaschek, W.: Psychic Components of Hyperemesis Gravidarum and Their Treatment, p. 198.

Vol. 97, No. 8, February 25, 1955.

Schwaiger, M.: The Influence That Possible Malignant Degeneration Should Have on the Indication for Surgical Intervention in Benign Conditions, p. 224.

*Titles preceded by an asterisk are abstracted below.

Vol. 97, No. 9, March 4, 1955.

Kock, W.: Estrogen Levels in Animals Late in Pregnancy and at Parturition, p. 259.

Vol. 97, No. 13, April 1, 1955.

*Franken, H.: The Rh Factors and Their Practical Importance, p. 381.

Franken: The Rh Factors and Their Practical Importance, p. 381.

The blood group systems presently known are reviewed with special attention to the Rh factor. In view of the fact that the Rh antibody is acquired only in the presence of the antigen, erythroblastosis does not occur in the absence of previous transfusion or pregnancy. Prognosis for childbearing in Rh-negative women does not depend only on the phenotype of the partner. If the father is heterozygous for the Rh factor, there is a 50 per cent chance that the offspring will be Rh negative and hence unaffected by maternal antibodies. In addition, it appears empirically that even the Rh-positive offspring has a better prognosis.

Erythroblastosis is classified in three categories of anemia neonatorum, icterus gravis (with kernicterus), and hydrops fetalis, infants with the latter usually being stillborn.

It is emphasized that blood transfusions are not innocuous and should not be undertaken without indication. American statistics show a mortality of 1 in 3,000. To avoid untoward reactions, the following safeguards should be undertaken:

1. Direct transfusion should be done in serious emergency cases only so that donor blood can be tested for syphilis, malaria, and infectious hepatitis and leisurely typing and cross-matching can be done.

2. Whole blood should be used only when positively indicated. In many cases serum, plasma, plasma expanders, and physiological saline are adequate and less dangerous.

3. Typing, including Rh and cross-matching, must be done very carefully. Particularly in female children and women in the childbearing age, only Rh compatible blood should be used.

In addition to Rh testing of the husband, anti-Rh titers must be determined throughout pregnancy.

There is considerable dispute as to whether cesarean section at 38 or 39 weeks decreases fetal morbidity or mortality in the face of rising titers. On the other hand, the value of exchange transfusions is definitely established.

WALTER F. TAUBER, M.D.

Vol. 97, No. 14, April 8, 1955.

Hartenback, W.: The Importance of the Common Anticoagulants in Surgical Practice, p. 423.

Vol. 97, No. 17, April 29, 1955.

*Rendelstein, A. D.: The Etiology of Prolapse of the Female Genital Tract, p. 556.
*Waitz, R., and Bachmann, F. F.: Clinical Aspects of Genital Tuberculosis, p. 558.
Roemer, G. B.: Etiology and Prevention of Infectious Hepatitis, p. 561.

Rendelstein: Etiology of Prolapse of the Female Genital Tract, p. 556.

The etiology and pathogenesis of prolapsus uteri are discussed. Parity and "constitutional weakness" are mentioned only in passing as etiological factors. Emphasis is placed on the erect posture of man which puts a stress on the pelvic floor for which, philogenetically speaking, it was not intended. Disturbances in innervation such as is seen in spina bifida can be the cause of prolapse even in children. Intra-abdominal pressure is an important factor also. It is suggested, for example, that coughing in the immediate puerperium should be treated vigorously for that reason.

The pathogenesis of prolapse is described as follows: With the weakening of the vesicovaginal fascia, the trigone becomes somewhat dependent and a vicious cycle is set up

of an accumulation of urine and further distention of the trigone with an attendant weakening of the muscular action of the internal sphincter. Rectocele is formed in an analogous fashion with prolapse only following thereafter. It is pointed out that hypertrophy of the cervix, which is so frequently seen associated with prolapse, cannot be properly explained at this time.

WALTER F. TAUBER, M.D.

Waitz and Bachmann: Clinical Aspects of Genital Tuberculosis, p. 558.

Seventy-nine cases of tuberculosis of the female genital tract are discussed. There has been a sharp increase in the number of cases reported in Bavaria since the end of the war, largely due to better diagnostic methods, particularly bacteriological study of the menstruum.

Only 50 per cent of the patients were found to be sterile. In almost 50 per cent of the cases, the lesion was localized to the Fallopian tubes. In two cases, however, tubercular endometritis was found several years after bilateral salpingectomy.

WALTER F. TAUBER, M.D.

Vol. 97, No. 19, May 13, 1955.

*Patzer, H., and Stech, D.: Causes of Death in Icterus Gravis, p. 633.

Patzer and Stech: Causes of Death in Icterus Gravis, p. 633.

The pathology and causes of death in severe erythroblastosis are discussed, along with their importance to the handling of babies resulting from Rh-incompatible pregnancies. All cases, basically, present pictures of damage of capillary permeability and anaphylactic shock. Anemia; erythroblastosis; edema; cerebral, renal, hepatic, and splenic damage are purely secondary to them. Exchange transfusion is frequently helpful, but may be useless even in the absence of undue delay.

WALTER F. TAUBER, M.D.

Vol. 97, No. 20, May 20, 1955.

*Busch, K.: The Influence of Metacresyl-Sulfonic Acid on Lesions and Inflammations of Vaginal Mucosa, p. 671.

Busch: Influence of Metacresyl-Sulfonic Acid on Lesions and Inflammations of Vaginal Mucosa, p. 671.

The use of formalin-polymerized metacresyl-sulfonic acid for vaginal discharge, nonspecific vaginitis, cervicitis, and cervical erosion is advocated. Based on its acidity (pH 6.0), it selectively inhibits the growth of pathological vaginal flora and enhances that of the Döderlein bacillus. In mild and moderate cases, this treatment alone is sufficient. Sometimes, however, this treatment must be preceded by antibiotics or sulfonamides. Then the Döderlein bacillus must be introduced artificially because the previous therapy is nonselective in its bactericidal action. This agent is also useful in preoperative vaginal preparation.

WALTER F. TAUBER, M.D.

Vol. 97, No. 22, June 3, 1955.

*Knoerr, K.: Clinical Observation on the Use of 17-Methylestradiol, p. 734.
Voss, H. E.: The Enteric Effectiveness of Estradiol Derivatives: 17-Methylestradiol, p. 735.

Knoerr: Clinical Observation on the Use of 17-Methylestradiol, p. 734.

The oral administration of 17-methylestradiol in a large number of cases has shown that good estrogenic effect can be obtained by this route, in all cases where substitution for the hormone of the Graafian follicle is indicated.

WALTER F. TAUBER, M.D.

Vol. 97, No. 25, June 24, 1955.

*Dietsch, H.: Electrocoagulation in Nonmalignant Dysfunctional Bleeding, p. 822.
*Ludwig, K. H.: Mercaptans in Gynecological Radiotherapy, p. 823.

Dietsch: Electrocoagulation in Nonmalignant Dysfunctional Bleeding, p. 822.

Cautery of the endometrial cavity is advocated for the treatment of menopausal bleeding and hypermenorrhea, proved benign, which have not responded to simple curettage. The advantage of this method over x-ray or radium castration lies in the preservation of ovarian function. Contraindications are malignancy of the endometrium, pelvic inflammatory disease, bleeding secondary to ovarian neoplasm, puerperium or postabortal state, and submucous myomas. Sterility does not result from this procedure and menstrual function can continue.

WALTER F. TAUBER, M.D.

Ludwig: Mercaptans in Gynecological Radiotherapy, p. 823.

The incidence and severity of radiation sickness can be reduced by administration of cysteine and other amino acids containing the thiol radical. While the pathophysiology of radiation sickness is not yet settled, it is felt that certain enzyme systems containing the mercaptan-amino acids are destroyed in radiation and can be protected by SH-radical.

WALTER F. TAUBER, M.D.

Surgery, Gynecology and Obstetrics

Vol. 100, June, 1955.

*White, T. T.: Prognosis of Breast Cancer for Pregnant and Nursing Women, p. 661.
Baker, K.: Vaginal Delivery After Lower Uterine Cesarean Section, p. 690.

White: Prognosis of Breast Cancer for Pregnant and Nursing Women, p. 661.

Analysis is made of 1,413 cases of breast carcinoma complicated by pregnancy and lactation. The author found the incidence of this complication to be only 2.8 per cent in 45,881 breast malignancies.

The survival rate of women treated for breast carcinoma who later become pregnant is comparable to that of women with uncomplicated carcinoma of the breast. Likewise, the survival rate for women treated for breast carcinoma while pregnant or nursing was found to be comparable to that of women with uncomplicated cancer of the breast in the absence of metastases, but worse, if spread had already occurred.

The cases found among the pregnant or nursing women were more advanced than those encountered in the general group.

In the author's opinion, no concrete evidence could be found in this series of patients to show that any benefit accrued from abortion.

VINCENT TRICOMI, M.D.

Vol. 101, July 1955.

*Hon, Edward H., and Morris, J. McL.: Gonadotrophin Titers in Disturbed Pregnancies, p. 59.

Hon and Morris: Gonadotrophin Titers in Disturbed Pregnancies, p. 59.

A study of urinary gonadotrophins was made, employing the North American male toad, Bufo americanus. The authors conclude that the toad system is practical and accurate and provides a rapid test for diagnosis and prognosis in problems related to urinary gonadotrophin titers and suspected alterations of pregnancy.

In all cases studied, in which the chorionic gonadotrophin titers were less than 3,000 I.U. per 24 hours from 50 to 90 days after the first day of the last normal menstrual period, the pregnancy ended in abortion.

VINCENT TRICOMI, M.D.

Vol. 101, August, 1955.

*Sykes, M. P., Rundles, R. W., Pierce, V. K., and Karnofsky, D. A.: Triethylene Melamine in the Management of Far Advanced Ovarian Carcinoma, p. 133.

Sykes, Rundles, Pierce, and Karnofsky: Triethylene Melamine in Management of Far Advanced Ovarian Carcinoma, p. 133.

Triethylene melamine (TEM) was employed as the therapeutic agent in the treatment of 26 patients with far-advanced and inoperable recurrent carcinoma of the ovary. Fourteen (54 per cent) obtained some degree of improvement subjectively and, of these, 8 (31 per cent) also showed evidence of tumor regression. On this basis, the triethylene melamine is indicated as a palliative measure in such patients. The chemotherapeutic agent may be administered before, after, or at the time of x-ray therapy.

VINCENT TRICOMI, M.D.

Wiener Medizinische Wochenschrift

Vol. 105, No. 13, April 2, 1955.

Fuchs, G.: X-ray Therapy and X-ray Injuries, p. 253.

Vol. 105, No. 18, May 7, 1955.

Siems, K. J.: Some New Points on the Diagnosis and Development of Occiput Posterior, p. 362.

Vol. 105, Nos. 20-21, May 21, 1955.

Heidler, H.: The History of the Diagnosis of Pregnancy, p. 402.
*Beyreder, J., and Herzog, E.: Clinical Experiences With a New Oral Diuretic, p. 408.
*Demmer, F.: Sponge Count, p. 418.
Jirasek, A.: Are Present Methods of Autopsy Adequate for the Surgeon? p. 428.

Beyreder and Herzog: Clinical Experiences With a New Oral Diuretic, p. 408.

An evaluation of Diamox is presented in 71 cases of water retention, with a favorable response in 56. Most of these patients had heart disease. This drug acts through inhibition of carbonic acid anhydrase in the kidney tubule, favoring the excretion of sodium and, hence, of water. In therapeutic doses no toxicity is noted, although acidosis is possible. Cirrhosis is a contraindication for the use of Diamox. Patient response is not uniform and can be determined only after clinical trial in each case.

WALTER F. TAUBER, M.D.

Demmer: Sponge Count, p. 418.

The author presents several cases in which presumably missing sponges could not be found in the abdomen and were usually found elsewhere later and, conversely, cases in which, despite supposedly correct sponge counts, sponges were left behind. He suggests the following precautions: (1) discontinue counting sponges and leave the surgeon solely responsible on the question of foreign bodies; (2) have an instrument attached to all sponges and similar material used in the abdomen; (3) as far as possible, abandon the use of surgical sponges in favor of laparotomy sponges.

WALTER F. TAUBER, M.D.

Vol. 105, No. 22, June 4, 1955.

Oehlinger, L.: Our Experiences With Hysterosalpingography, p. 451.

Vol. 105, Nos. 25-26, June 25, 1955.

Bergmann, H.: Laboratory Tests and Greater Safety in Blood Transfusions, p. 502.
*Halter, G.: Symptomatology and Treatment of Pelvic Inflammatory Disease, p. 505.
Rossboth, W.: Pain and Spasms in Labor, p. 526.

Halter: Symptomatology and Treatment of Pelvic Inflammatory Disease, p. 505.

The author reviews the symptoms and differential diagnosis of acute pelvic inflammatory disease, and discusses its treatment. There is occasional difficulty in distinguishing pelvic inflammatory disease from appendicitis or ectopic pregnancy. Location, erythrocyte sedimentation rate, and temperature are frequently helpful. Sometimes an exploratory laparotomy must be undertaken to establish a definite diagnosis. If, in such cases, salpingitis is found, the abdomen should be closed immediately.

For most cases conservative therapy is recommended and it is suggested that penicillin is potentiated by the use of sulfonamides. In the presence of abscesses, the systemic use of chemotherapy is useless. The author has obtained good results with aspiration through the pouch of Douglas and local instillation of antibiotics and sulfonamides. In some cases, this procedure has to be repeated several times. If a frozen pelvis is encountered in such cases, hyaluronidase is also instilled. Laparotomy is indicated in only three types of cases: (1) difficult diagnostic problems, (2) abdominal catastrophe (rupture of pyosalpinx or tubovarian abscess, or intestinal obstruction due to adhesions), (3) chronic pelvic inflammatory disease, unresponsive to conservative treatment. In the latter, surgery is undertaken only in a completely quiescent phase and complete extirpation of the genital tract gives the best results.

WALTER F. TAUBER, M.D.

Acta Geneticae, Medicae et Gemellologiae

Vol. 4, No. 3, September, 1955.

Gedda, L.: Genetic Evaluation of Athletes. (Italian), p. 249.
Blaizot, A. M., and Tisserand-Perrier, M.: The Sketch as a Method of Personality Investigation in Identical Twins. (French), p. 261.
Grebe, H.: Sports and Twins. (German), p. 275.
Pändler, U.: The Hereditary Mechanism of Dupuytren's Contracture. (French), p. 296.
*McKeown, T., and MacMahon, B.: Infantile Hypertrophic Pyloric Stenosis: Data on 81 Pairs of Twins. (English), p. 320.
Wendt, G. G.: The "Individuelle Musterwert" of Fingerprints and Heredity. (German), p. 330.
*Vulpis, N.: Study of the Genetic Linkage Between Mediterranean Anemia and the Rh System. (Italian), p. 338.
Pelliccioli, V., and Garioni, F.: Petit Mal Epilepsy in Two Monozygotic Twins. The Application of the EEG to the Study of Heredity in Epilepsy. (Italian), p. 342.
Schulee, J. E.: The International Congress of Twins at Oirschot. (French), p. 358.
Bruins, J. W.: European Congress of Twins. (English), p. 360.

McKeown and MacMahon: Infantile Hypertrophic Pyloric Stenosis, p. 320.

The author analyzes 81 pairs of twins. He feels this is a representative sample of a twin universe because it contains the expected proportion of monozygotic twins to dizygotic twins. The incidence of hypertrophic pyloric stenosis in births of the general population was 0.3 per cent. The development of this condition in a twin partner of an affected twin was 8.6 per cent and 5.8 per cent in a sibling of the affected twin.

FRANCIS B. O'BRIEN, M.D.

Vulpis: Study of the Genetic Linkage Between Mediterranean Anemia and the Rh System, p. 338.

The author studied 16 families, the members of which had some clinical form of Mediterranean anemia. He did serological tests for C.c.D.E., and concluded that there is a strong genetic linkage within each system; viz., Rh and Mediterranean anemia. They act independently of each other, however, and there is no genetic basis to explain a linkage between both systems.

FRANCIS B. O'BRIEN, M.D.

American Journal of the Medical Sciences

Vol. 230, No. 1, July, 1955.

*Moyer, John H., Hughes, Warren, Dennis, Edward, Beazley, H. Liston, and McConn, Robert: Results With a Combination of Rauwolfia and Adrenergic Blockade in the Treatment of Hypertension, p. 33.

*Andreae, Eric, and Smith, Frank Edward: The Effect of Oral Reserpine on Renal Plasma Flow in Hypertension, p. 45.

*Olmstead, Edwin G., Cassidy, James E., and Murphy, Francis D.: The Use of Beer in the Low-Salt Diet With Special Reference to Renal Disease, p. 49.

Moyer, Hughes, Dennis, Beazley, and McConn: Results With a Combination of Rauwolfia and Adrenergic Blockade in the Treatment of Hypertension, p. 33.

Forty-seven hypertensive patients were divided into two groups; 19 were treated with a combination of Rauwolfia and phenoxybenzamine and 28 with these drugs plus protoveratrine. In the first group, Rauwolfia given alone for three months or more had not reduced the blood pressures to normal (150/100). The addition of protoveratrine had very little further effect. There was a significant reduction in the blood pressure in 82 per cent of the cases; the effect was independent of the severity of the hypertension. The addition of Rauwolfia reduced the required dose of phenoxybenzamine by nearly 90 per cent and seemed to lessen the orthostatic hypotension but had little effect upon the other side reactions. Side effects included nasal congestion, sedation, fatigue, increased appetite, dizziness, and bradycardia. "The combination of phenoxybenzamine and rauwolfia . . . may prove generally useful in the treatment of all degrees of hypertension."

LEON C. CHESLEY, PH.D.

Andreae and Smith: Effect of Oral Reserpine on Renal Plasma Flow in Hypertension, p. 45.

Fifteen patients with essential hypertension, five men and ten women, were selected for study. The renal plasma flow was measured in each case before any hypotensive drug was used; the patients were then given oral Reserpine for two to five months. At the end of this time no significant changes were found in the blood pressure, heart size, electrocardiogram, or renal plasma flow.

LEON C. CHESLEY, PH.D.

Olmstead, Cassidy, and Murphy: Use of Beer in the Low Salt Diet With Special Reference to Renal Disease, p. 49.

Five patients with glomerulonephritis, two with Kimmelstiel-Wilson disease, and two with malignant hypertension were studied before and after the addition of beer to a low-salt diet. A liter of beer provides about 420 calories, 28 Gm. of protein, 44 Gm. of carbohydrate, and contains only about 30 mg. of sodium. The addition of beer increases the palatability of the low-salt diet, and there was no evidence from either the clinical or laboratory standpoint that it had any deleterious effect upon the renal disease.

LEON C. CHESLEY, PH.D.

British Medical Journal

Vol. 2, Sept. 17, 1955.

*Gibson, George B.: Prolonged Pregnancy, p. 715.

*Gordon, Ronald R., and Dean T.: Fetal Deaths From Antenatal Anticoagulant Therapy, p. 719.

Gibson: Prolonged Pregnancy, p. 715.

In establishing the diagnosis of prolonged pregnancy the following factors may be of value: the intelligence of the patient and the accuracy of her observations, the length of her menstrual cycles, the size of the uterus when examined early in pregnancy, the date

of quickening, and in retrospect the weight of the baby at birth. Five thousand unselected and essentially consecutive cases were evaluated by one examiner at two Belfast hospitals.

The average duration of pregnancy was from two days prior to the estimated date of delivery to one week after the expected date. If the estimated date of delivery was calculated according to Nägele's rule from the last instead of the first day of the last menses, the actual day of delivery would correspond more closely to the estimated date. The length of the menstrual cycles did not appear to influence the length of the gestation. Fetal mortality was minimal during the forty-first and forty-second weeks, doubled during the forty-third week, and tripled thereafter.

The author attempts to explain the reason for this increased fetal mortality in the later weeks. Babies showed no significant weight variations as has been suggested by current investigators. Trauma likewise did not seem to be a factor in increasing the mortality. A considerable number of the fetal deaths did occur either intra partum or through failure to establish respirations in spite of a strong heartbeat after delivery. Anoxia occurs during the first and second stages of labor.

In the treatment of prolonged pregnancy induction of labor has been instituted in some clinics after the diagnosis has been made. In the experience of the author, however, medical induction has not been successful unless labor was about to start spontaneously. Conflicting reports have been presented regarding the safety of the surgical approach to induction and the author ardently objects to the current methods. Instead of these, he prefers to examine his patients, and, should the vertex be well engaged and the cervix partially effaced, then assurance of the expectant mother that labor will soon commence naturally should suffice. Should the head not be fixed in the pelvis, stripping the membranes and a hot vinegar douche may be adequate stimulation to induce labor.

Once labor has started frequent and careful attendance upon the patient must be the rule and at the first sign of fetal distress delivery either by forceps or cesarean operation should be performed.

ARTHUR PERELL, M.D.

Gordon and Dean: Fetal Deaths From Antenatal Anticoagulant Therapy, p. 719.

Antenatal thrombophlebitis is a rarity. When it does exist, however, treatment or prophylaxis with the standard anticoagulants must be undertaken with the greatest of caution in view of the fetal dangers reported even when prothrombin levels were controlled. A case history of a twin gestation in which there was a clear-cut indication for the use of anticoagulants is reported. One of the infants died in utero and the second at the age of 35 days. Postmortem examinations revealed the cause of the demise in both instances to be secondary to the drug administered to the mother. Other previously reported cases are discussed.

After considering the various methods of determining the prothrombin level the authors summarize, with the following conclusions: (1) The maternal mortality associated with thrombophlebitis in pregnancy is not great enough to warrant the routine use of anticoagulant therapy. (2) Should the mother suffer from multiple pulmonary emboli, then the serious fetal risk must be taken into consideration. If the decision to employ anticoagulants is reached, then prothrombin levels should be checked by both the one- and two-stage methods of determination.

ARTHUR PERELL, M.D.

Correspondence

Modification in Pneumocography Technique

To the Editors:

With the cooperation and assistance of Dr. B. S. Abrams (Pneumocography as an Aid in the Diagnosis of Gynecologic Disease, AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY **70:** 1115, 1955) a simplifying modification in technique has been adopted. A Wiseman Gynograph using a "Sparklets" cartridge (7-9 Gm. dry CO_2, expanded volume 3,500-4,500 c.c.) is used as the source of carbon dioxide, which is permitted to flow into the abdominal cavity through the machine and attached paracentesis needle at a pressure of not over 250 mm. Hg. Flow pressure is kept low until the success of the puncture is assured. It is then increased to the limits maintaining the flow so that its pressure never exceeds the safety valve escape pressure. Injection is completed in less than 2 to 3 minutes, and pressure symptoms, should they occur, are minimal and disappear within 15 to 30 minutes, by which time the procedure has been completed. The patient is then returned to her room for discharge at any time after interpretation of the films. Clear and easily read films are standard, and there has been no adverse effect in any subject.

EDUARD EICHNER, M.D.

10605 CHESTER AVENUE
CLEVELAND 6, OHIO
MAY 22, 1956

Items

American Board of Obstetrics and Gynecology

Applications for certification (American Board of Obstetrics and Gynecology) for the 1957 Part I Examinations are now being accepted. All candidates are urged to make such application at the earliest possible date. Deadline date for receipt of applications is Oct. 1, 1956.

All candidates for admission to the Examinations are required to submit with their application a plain typewritten list of all patients admitted to the hospitals where they practice, for the year preceding their application or the year prior to their request for reopening of their application.

Application for re-examination, as well as requests for resubmission of case abstracts, must also be made to the Secretary prior to Oct. 1, 1956.

Current Bulletins outlining present requirements may be obtained by writing to the Secretary's office.

ROBERT L. FAULKNER, M.D., SECRETARY
AMERICAN BOARD OF OBSTETRICS AND GYNECOLOGY
2105 ADELBERT ROAD
CLEVELAND 6, OHIO

Ninth All India Obstetric and Gynaecological Congress

The Ninth All India Obstetric and Gynaecological Congress will be held in Amritsar, Dec. 29, 30, and 31, 1956. The main subjects for discussion will be: (1) Cardiac Disease Complicating Pregnancy. (2) Malignancies of the Body of the Uterus. (3) Statistical Survey of (a) Eclampsia and (b) Menarche and Menopause.

Those who desire to read papers should communicate by Sept. 1, 1956, with Dr. B. L. Kapur, Honorary Secretary, Obstetric and Gynaecological Society of Northern India, Benjamin Road, Ludhiana.

Pan-Pacific Surgical Association

The Seventh Congress of the Pan-Pacific Surgical Association will be held in Honolulu, Hawaii, Nov. 14-22, 1957. All members of the profession are cordially invited to attend and are urged to make arrangements as soon as possible if they wish to be assured of adequate facilities.

A scientific program by leading surgeons with sessions in all divisions of surgery and related fields promises to be of interest to all doctors.

Further information and brochures may be obtained by writing to Dr. F. J. Pinkerton, Director General of the Pan-Pacific Surgical Association, Room 230, Young Building, Honolulu, Hawaii.

International Cancer Cytology Congress

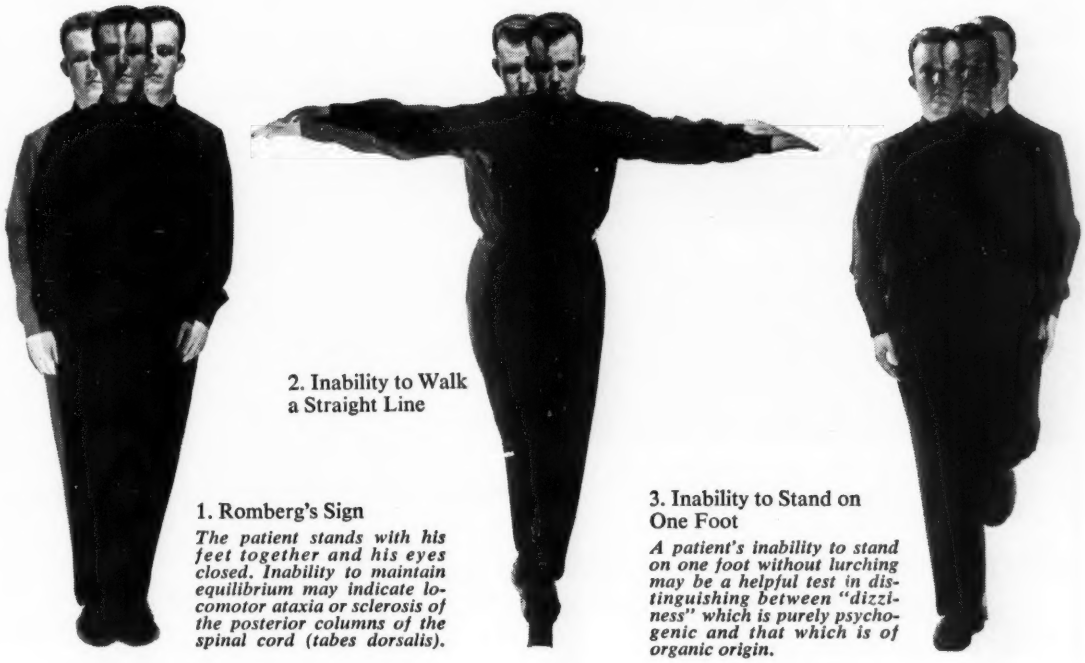
The 1956 International Cancer Cytology Congress will be held at the Drake Hotel in Chicago, Illinois, Oct. 8 to 13, 1956.

This Congress, the first of its kind, will be sponsored by the American Society of Clinical Pathologists, the College of American Pathologists, the Intersociety Cytology Council, and the International Union Against Cancer. The first three organizations have a combined membership of approximately three thousand pathologists and other physicians.

The general theme of the Congress will be Exfoliative Cytology and the program to be presented during this period will stress but not be devoted exclusively to the subject of Exfoliative Cytology in all of its various aspects and its relationship to various specialties of medicine.

Notes on the Diagnosis and Management of "Dizziness"

II. False Dizziness



1. Romberg's Sign

The patient stands with his feet together and his eyes closed. Inability to maintain equilibrium may indicate locomotor ataxia or sclerosis of the posterior columns of the spinal cord (tabes dorsalis).

2. Inability to Walk a Straight Line

3. Inability to Stand on One Foot

A patient's inability to stand on one foot without lurching may be a helpful test in distinguishing between "dizziness" which is purely psychogenic and that which is of organic origin.

False dizziness is a sensation of sinking or lightheadedness which is often of psychogenic origin. It should be distinguished from true "dizziness" or vertigo[1] in which there is a definite whirling, moving sensation.

Unsteadiness, lightheadedness and similar manifestations of false dizziness[2] may be psychogenic or the result of arteriosclerosis, hypoglycemia, drug sensitivity and general metabolic disturbances such as anemia and malnutrition. Hypertension is often the cause of these symptoms.

Psychogenic dizziness probably originates at the highest brain centers. It may be described as a sense of uncertainty with occasional mild lurching but not to the point of falling. In these patients there is no nausea, no disturbance of vestibular pathways and otologic and neurologic examinations are negative. The sensation is unaffected by head movement. Symptoms usually disappear[3] with complete rest.

Dramamine® has been found highly effective in many of the conditions already mentioned. Maintenance therapy with Dramamine will often keep the patient from becoming incapacitated by his condition.

Dramamine is also a standard for the management of motion sickness and is useful for relief of nausea and vomiting of fenestration procedures and radiation sickness and for relief of "true dizziness" of other disorders.

Dramamine (brand of dimenhydrinate) is supplied in tablets (50 mg.) and liquid (12.5 mg. in each 4 cc.). G. D. Searle & Co., Research in the Service of Medicine.

1. Swartout, R., III, and Gunther, K.: "Dizziness:" Vertigo and Syncope, GP *8*:35 (Nov.) 1953.

2. DeWeese, D. D.: Symposium: Medical Management of Dizziness. The Importance of Accurate Diagnosis, Tr. Am. Acad. Ophth. *58*:694 (Sept.-Oct.) 1954.

3. Kunkle, E. C.: Central Causes of Vertigo, J. South Carolina M. A. *50*:161 (June) 1954.

SEARLE

PROVEN
PAIN CONTROL
with safety

GRADATIONS OF ANALGESIA

'TABLOID' 'EMPIRIN' COMPOUND®
Acetophenetidin gr. 2½, Acetylsalicylic Acid gr. 3½, Caffeine gr. ½

'TABLOID' 'EMPIRIN' COMPOUND
with CODEINE PHOSPHATE gr. ⅛, No. 1 (N)

'TABLOID' 'EMPIRIN' COMPOUND
with CODEINE PHOSPHATE gr. ¼, No. 2 (N)

'TABLOID' 'EMPIRIN' COMPOUND
with CODEINE PHOSPHATE gr. ½, No. 3 (N)

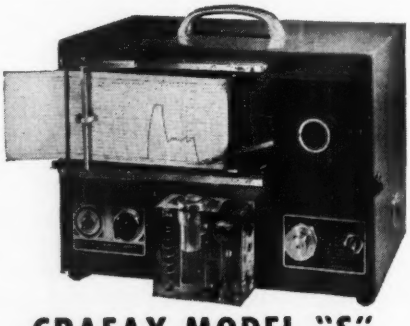
'TABLOID' 'EMPIRIN' COMPOUND
with CODEINE PHOSPHATE gr. 1, No. 4 (N)

(N) subject to Federal Narcotic Law

BURROUGHS WELLCOME & CO. (U.S.A.) INC.
Tuckahoe, N. Y.

The Dickinson Research Memorial, research arm of the Planned Parenthood Federation of America, Inc., is interested in supporting basic research in the physiology of reproduction, with special emphasis on factors influencing fertility. For further information address the Dickinson Research Memorial, 501 Madison Avenue, New York 22, New York.

HAILED BY DOCTORS EVERYWHERE
FOR SIMPLICITY, ACCURACY & SAFETY



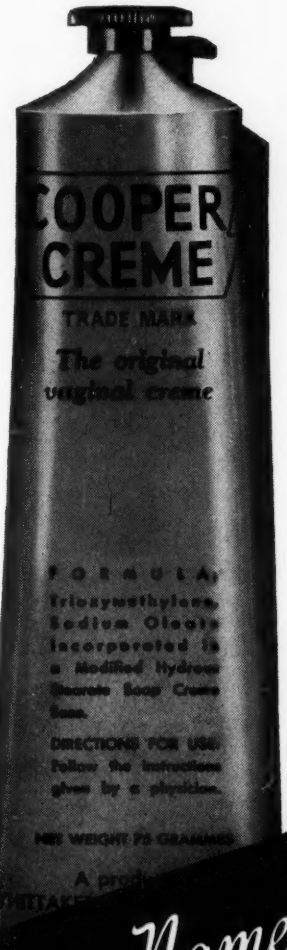
GRAFAX MODEL "S"
KYMOINSUFFLATOR
FOR TUBAL INSUFFLATION

- Permanent records—400 tests per roll
- Standard cylinder contains CO_2 for 500 tests
- Controlled adjustable maximum pressure
- Lowest in cost—to buy, operate and maintain
- Compact & portable—weighs only 16 lbs.

Send for descriptive literature

GRAFAX INSTRUMENT CO., Dept. G
32 E. 10th St.
New York 3, New York

This is the
ORIGINAL
contraceptive
creme
with a record of
22 years
of successful use!



No Finer Name in Contraceptives...

WHITTAKER LABORATORIES, INC.
Peekskill, New York

PROVEN
PAIN CONTROL
with sedation

GRADATIONS OF ANALGESIA
with light sedation

'EMPIRAL'®

Phenobarbital	gr. ¼
Acetophenetidin	gr. 2½
Acetylsalicylic Acid	gr. 3½

'CODEMPIRAL'® No. 2(N)

Codeine Phosphate	gr. ¼
Phenobarbital	gr. ¼
Acetophenetidin	gr. 2½
Acetylsalicylic Acid	gr. 3½

'CODEMPIRAL'® No. 3(N)

Codeine Phosphate	gr. ½
Phenobarbital	gr. ¼
Acetophenetidin	gr. 2½
Acetylsalicylic Acid	gr. 3½

(N) subject to Federal Narcotic Law

BURROUGHS WELLCOME & CO. (U.S.A.) INC.
Tuckahoe, N. Y.

The terrible vengeance of Joseph P. Fyffe

ON A WARM August evening in 1870, a footsore stranger in naval officer's uniform walked into East Haddam, Connecticut.

His name was Joseph P. Fyffe, and he was revenging himself on the Navy for refusing to advance him travel money to proceed to his new station, San Francisco.

He was trudging cross-country *on foot.* And conscientiously wiring in daily progress reports well-calculated to give his superiors apoplexy. His sixth, from Albany, N.Y., read in part:

> *"Entered Albany barefooted X Comfortable X Earning my keep as bartender X Local rum far superior that served in Navy X Am sending sample"*

At this, the Navy struck its colors, reversed its time-honored tradition, and began prepaying travel allowances.

Strangely enough, Joe Fyffe actually wound up as a rear admiral. That, of course, was years later; and he has long since passed to his reward. But his vigorous and outspoken independence is still alive and kicking in today's Americans. That's why our country is a strong, vital nation and why our country's Savings Bonds are one of the finest investments in the world.

165 million Americans stand behind U. S. Savings Bonds. *There is no better guarantee.* So buy Bonds regularly—and keep the ones you buy.

It's actually easy to save—when you buy Series E Savings Bonds through the Payroll Savings Plan. Once you've signed up at your pay office, your saving is done *for you.* The Bonds you receive pay good interest—3% a year compounded half-yearly when held to maturity. And the longer you hold them, the better your return. Even after maturity, they go on earning 10 years more. So hold on to your Bonds! Join Payroll Savings today—or buy Bonds where you bank.

Safe as America—
U.S. Savings Bonds

The U.S. Government does not pay for this advertisement. It is donated by this publication in cooperation with the Advertising Council and the Magazine Publishers of America.

What makes cancer MAN'S CRUELEST ENEMY?

SOME diseases kill us mercifully.

NOT CANCER. Yet, if nothing is done, 23 million living Americans are destined to die of cancer . . . 230,000 of them *this year.*

SOME diseases reveal their beginnings by pain or fever or shock. Not cancer. It starts silently, secretly, and too often spreads rapidly.

AND SOME diseases spare us our young people. Not cancer! It strikes men and women and children, the old and the young. If nothing is done, one American in five will be stricken with cancer.

SOMETHING CAN BE DONE. You can strike back at this cruel killer with a really generous gift to the American Cancer Society. Your money is *urgently* needed—for research, for education, for clinics and facilities. Please make it a really BIG gift!

Cancer
MAN'S CRUELEST ENEMY
Strike back—Give
AMERICAN CANCER SOCIETY

THE SOURCE OF RE-INFECTION CAN BE

THE HUSBAND

IN VAGINAL TRICHOMONIASIS

"THE available evidence indicates that one of every four or five adult women harbor the parasite."[1] In many cases coitus must be regarded as a method of transfer.[2]

Infests the male, too—"The infestation in males is probably more common than realized and will more frequently be recognized. . . ."[3] Karnaky reports the infection in the urethra, in the prostate or under the prepuce of 38 among 150 husbands with infected wives.

Symptoms often absent—In the female, trichomonas vaginitis is a well recognized condition . . . but in the infected males symptoms are usually absent.[2] Or the infection causes little concern because it is transient and mild.

Prevent re-infection—"Eradication of the parasites in both sexual partners is of course ideal . . . obviously a condom is the most effective mechanical barrier."[1]

Prescription of prophylactics—To prevent re-infection take special measures to win the co-operation of the husband when you prescribe a prophylactic. Writing for *Schmid* prophylactics assures high quality, makes purchase less embarrassing.

If there is anxiety that the prophylactic might dull sensation, prescribe XXXX (FOUREX)® membrane skins, pre-moistened, and like the patient's own skin. For those who prefer a rubber prophylactic, prescribe RAMSES®—transparent, tissue-thin, yet strong. Suggest its use for four to nine months after the wife is trichomonad-free.

References: 1. Trussell, R. E.: Trichomonas Vaginalis and Trichomoniasis, Springfield, Ill., Charles C Thomas, 1947. 2. Lanceley, F., and McEntegart, M. G.: Lancet *1*:668 (April 14) 1953. 3. Strain, R. E.: J. Urol. *54*:483 (Nov.) 1945. 4. Karnaky, K. J.: Urol. & Cutan. Rev. *48*:812 (Nov.) 1938.

JULIUS SCHMID, INC., *Prophylactics Division*
423 West 55th Street, New York 19, New York

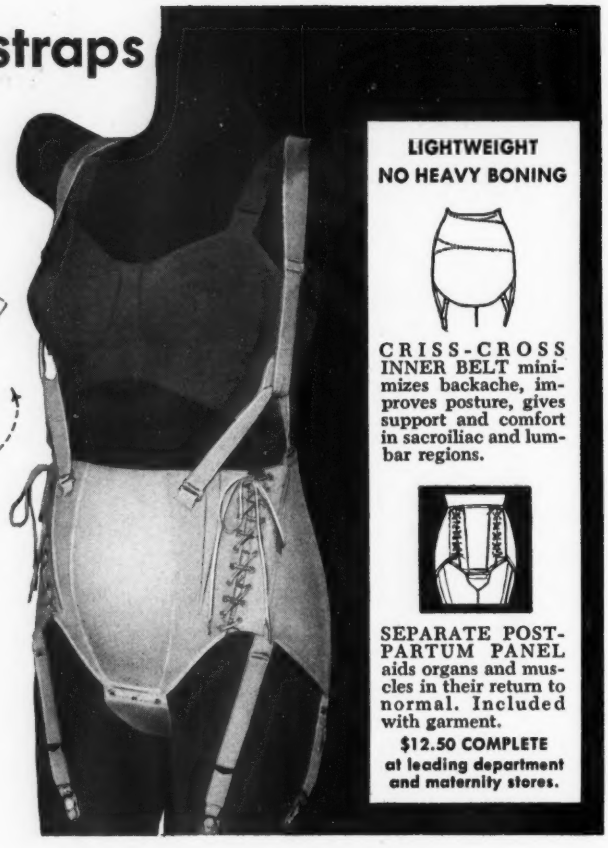
Nu-lift's* shoulder straps

GIVE NATURAL "HAMMOCK" SUPPORT, GREATER COMFORT

LEFT: Unsupported pregnancy: Baby's head low in pelvis. Bladder pressure, stretching of abdomen, acute angle of the back.

RIGHT: Nu-Lift supported Pregnancy: Baby is elevated, body is erect, intra-pelvic pressure lessened. Bulging, stretching minimized, backache relieved, possibility of varicosities lessened.

* PATENT #2,345,760



LIGHTWEIGHT NO HEAVY BONING

CRISS-CROSS INNER BELT minimizes backache, improves posture, gives support and comfort in sacroiliac and lumbar regions.

SEPARATE POST-PARTUM PANEL aids organs and muscles in their return to normal. Included with garment.

$12.50 COMPLETE
at leading department and maternity stores.

Nu-lift **MATERNITY SUPPORTS and brassieres**

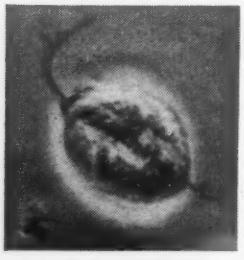
LITERATURE AND SAMPLE AVAILABLE UPON REQUEST

NU-LIFT COMPANY, INC.
Dept. J-8, 1021 N. Las Palmas, Hollywood 38, Calif.

HOW DAVIS TECHNIQUE

EXPLODES

HIDDEN TRICHOMONADS



Too often treatment fails to cure vaginal trichomoniasis because parasites survive and set up new foci of infection.

Now you can overcome this problem with VAGISEC® liquid and jelly, using the Davis technique.† VAGISEC liquid dissolves mucinous materials, penetrates thoroughly, and quickly reaches and explodes the hidden trichomonads.

Proved highly effective. VAGISEC liquid (originally "Carlendacide") is the formula developed by Dr. Carl Henry Davis, noted gynecologist and author, and C. G. Grand, research physiologist.[1] Clinical data show better than 90 per cent success with VAGISEC.[2]

Overwhelmingly powerful. VAGISEC liquid explodes trichomonads within 15 seconds of contact![3] One chelating agent and two surface-acting agents, combined in balanced blend, attack the parasite to weaken the cell membrane, to remove waxes and lipids, and to denature the protein. With its cell wall destroyed, the trichomonad imbibes water, swells and explodes.

The Davis technique. VAGISEC liquid, as a vaginal scrub, is used in office therapy. VAGISEC liquid and jelly are for home use.

Prevent re-infection. Many wives become re-infected because husbands harbor trichomonads.[2] To prevent re-infection, prescribe the protection afforded by Schmid high quality prophylactics – the superior RAMSES® rubber prophylactic, transparent and tissue-thin, yet strong, or XXXX (FOUREX)® skins of natural animal membrane, pre-moistened.

References: 1. Davis, C. H., and Grand, C. G.: Am. J. Obst. & Gynec. *68*:559 (Aug.) 1954. 2. Davis, C. H.: West. J. Surg. 63:53 (Feb.) 1955. 3. Davis, C. H.: J.A.M.A. *157*:126 (Jan. 8) 1955.

†Pat. App. for

JULIUS SCHMID, INC.
Gynecological Division
423 West 55th St., New York 19, N. Y.

END THE TORTURE

of agonizing vulvar itch in monilial vaginitis!

FAST, WELCOME RELIEF
HIGH RATE OF CURE

gentia·jel®

Vaginal Anti-infective Jelly. Contains 0.1% gentian violet in an acid polyethylene glycol base.

***Once* nightly — *just* 12 applications usually cures the most stubborn case**

GA-4

WESTWOOD PHARMACEUTICALS • Div. Foster-Milburn Co. • 468 Dewitt St., Buffalo 13, N. Y.

Breast Feeding is Easy and Comfortable with

Leading Lady's "NURSING MOTHER" BRA

New mothers enjoy comfortable, easy nursing with this *drop cup* bra. The large breast opening doesn't bind. An *inner band* gives healthful support underneath bust. Elastic diaphragm inset for expansion and easy breathing. Soft, washable flannel shields with water-proof *vinyl* facing prevent moisture stain. Of fine white cotton broadcloth.

Leading Lady BRASSIERE CO. Dept. J
2036 E. 105th St. • Cleveland 6, Ohio

Recommended by Many Leading Obstetricians
•
Write Today for Additional Information

Litzenberg-McLennan's Synopsis of

OBSTETRICS

Obstetrics—both normal and abnormal—is covered quite fully, and of necessity, quite succinctly, in this small, handy book. The chapters on physiology of pregnancy and physiology of labor are especially interesting; the pages devoted to control of pain in labor are noteworthy—and the many illustrations cover completely all phases of obstetrics from anatomy of the pelvis through puerperal care and complications. Small enough to fit in your pocket, it is clear and complete enough to serve as a steady reference. *Fourth Edition, 378 Pages, 157 Illustrations (6 in color), Price, $5.50.* The C. V. MOSBY CO., Publishers, St. Louis.

Booklet for patients

Your Care during Pregnancy

Practicing physicians are invited to ask for sample copy without obligation. Medically sponsored text. Used for a decade by thousands of leading doctors throughout United States and Canada. Write—

CADUCEUS PRESS
222 Nickels Arcade, Ann Arbor, Mich.

for normal, healthy, comfortable pregnancies

PHOSPHORUS-FREE, HIGH-POTENCY DRY-FILL* CAPSULES WITH "BUILT-IN" ANTIANEMIA FACTORS

*Micropulverized dry powder fill, for better toleration, faster assimilation and absence of fishy after-taste.

Walker LABORATORIES, INC., MOUNT VERNON, N. Y., U. S. A.

INDEX TO ADVERTISERS

Please mention "The American Journal of Obstetrics and Gynecology" when writing to advertisers—it identifies you

Abbott Laboratories ---------- 28
American Bakers Association ---------- 18
American Cancer Society ---------- 59
American Sterilizer ---------- 51
Arnar-Stone Laboratories, Inc. ---------- 25
Ayerst Laboratories ---------- 12

Bell-Craig, Inc. ---------- 50
Borden Company, The ---------- Fourth Cover
Boyle & Company ---------- 22, 23
Burroughs Wellcome & Company (U.S.A.), Inc. ---------- 24, 56, 57

Caduceus Press ---------- 61
Ciba Pharmaceutical Products, Inc. ---------- Second Cover
Ciba Pharmaceutical Products, Inc. ---------- 26

Desitin Chemical Company ---------- 2
Dickinson Research Memorial, The ---------- 56

Eaton Laboratories ---------- 37, 46
Esta Medical Laboratories, Inc. ---------- 4
Ethicon, Inc. ---------- Insert between pp. 10, 11

Florida Citrus Commission ---------- 3

Geigy Pharmaceuticals ---------- 38, 39
Grafax Instrument Co. ---------- 56
Grant Chemical Company, Inc. ---------- 34

Hoffmann-La Roche, Inc. ---------- Insert between pp. 16, 17
Hoffmann-La Roche, Inc. ---------- 10

Leading Lady Brassiere Company ---------- 61
Lilly and Company, Eli ---------- 54
Lloyd Brothers, Inc. ---------- 44, 45

Massengill Company, The S. E. ---------- Insert between pp. 4, 5
Massengill Company, The S. E. ---------- Insert between pp. 44 and 45
Massengill Company, The S. E. ---------- 15, 47
Mead Johnson & Company ---------- 1

National Drug Company, The ---------- Insert between pp. 32, 33
Nu-Lift Company, Inc. ---------- 60

Organon, Inc. ---------- 7
Ortho Pharmacéutical Corporation ---------- 21, 31

Pitman-Moore Company ---------- 36

Riker Laboratories ---------- 17
Roerig & Company, J. B. ---------- 11
Roussel Corporation ---------- 41

Schering Corporation ---------- 19, 29
Schmid, Inc., Julius ---------- 59, 60
Searle & Company, G. D. ---------- 55
Sharp & Dohme ---------- 13, 33, 49
Sklar Manufacturing Company, J. ---------- 16
Smith, Kline & French Laboratories ---------- 5, 14, 30, 35

Tampax Incorporated ---------- 42

United States Savings Bonds ---------- 58

Walker Laboratories, Inc. ---------- 62
Warner-Chilcott Laboratories ---------- 9, 20
Webster Company, The William A. ---------- 32
Westwood Pharmaceuticals ---------- 61
White Laboratories, Inc. ---------- 43
Whittaker Laboratories, Inc. ---------- 57
Whittier Laboratories ---------- 52, 53
Winthrop Laboratories ---------- 27

While every precaution is taken to insure accuracy, we cannot guarantee against the possibility of an occasional change or omission in the preparation of this index.

either way you win with Bremil®

"heads"... because a BREMIL formula provides a *complete* nutritional intake that consistently promotes infant growth and development at or above accepted standards[1]; made with grade A milk.

"tails"... because the easily digested, efficiently utilized protein content of BREMIL (approximating that of breast milk) virtually eliminates excoriations due to ammonia dermatitis[1], and does not impose an excessive solute load on the immature kidney[2]

Standard Dilution

One level measure to 2 fluidounces of hot water. Mixes like a liquid. Costs no more than ordinary formulas requiring vitamin and carbohydrate supplementation. In 1-lb. tins at all drug outlets.

1. Oberman, J. W., and Burke, F. G.: M. Ann. District of Columbia 23:483, 1954. 2. Hill, L. F.: Am. J. Clin. Nutrition 3:75, 1955.

Borden's®

PRESCRIPTION PRODUCTS DIVISION
350 Madison Avenue, New York 17